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PERNICIOUS ANEMIA

By

FRANK A. EVANS, M.D.

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CONTENTS

PREFACE 7

CHAPTER I

DEFINITION AND CLASSIFICATION 9

CHAPTER II

OCCURRENCE 24

CHAPTER III

PATHOLOGICAL ANATOMY 34

CHAPTER IV

ETIOLOGY 44

CHAPTER V

CLINICAL DESCRIPTION 70

CHAPTER VI

DIAGNOSIS 108

CHAPTER VII

TREATMENT 127

CHAPTER VIII

PROGNOSIS 152

BIBLIOGRAPHY 158

INDEX 165

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In this study an attempt has been made to draw the clinical picture of pernicious anemia as understood at present, to reconsider treatment, and to discuss the more promising lines of study so far made on the etiology.

CHAPTER I

Definition and Classification

"Progressive pernicious anemia" is a term used to designate a most interesting and complex clinical condition, so called because it is invariably fatal and exhibits an anemia as one of its most outstanding features. Although earlier reports on cases of anemia had appeared, those by Addison in 1849 and later, and by Biermer in 1868 first stimulated interest in this condition and represent the first useful attempts to classify different forms of anemia. Both Addison and Biermer presented in their reports some cases which were not pernicious anemia as we know it today; but others studied by them were undoubtedly true cases of pernicious anemia, and it seems reasonable to suppose that it was the special features of this disease that first attracted their attention. For this reason, and because each author presented, as far as he went, an excellent picture of the clinical syndrome which may be recognized by the most exacting diagnostic criteria of today as true pernicious anemia, the coupling of these names with this disease as a way of designation would appear, so far at least as this consideration is concerned, wholly justified.

Because at times in the past the anemia has been considered the primary factor in the disease, and because practically the same type of anemia may be seen in other conditions, some confusion in classification of anemias, and some doubt as to the existence of perni-

cious anemia as a true clinical entity has arisen. Such questionings are in order and indeed it may be possible that additional studies will necessitate further revision of the present classification of anemias and eliminate entirely "pernicious anemia" as a separate and distinct clinical entity. To understand the exact status of the anemia in pernicious anemia it is necessary to discuss the nature of anemia in general, the various types encountered, and their classification.

The term *anemia* is used to mean a deficiency in the oxygen-carrying substance of the blood, hemoglobin. This may be manifested primarily by a diminution of the total amount of hemoglobin, or by a decrease in the number of red blood cells. It does not mean a lessened amount of blood, for a lowered blood volume has not been shown as a constant finding, even in the severest anemias, and changes in the blood volume may occur with no variations of moment in the total hemoglobin present. If the anemia is manifested primarily by a diminution of the total hemoglobin, the number of red blood cells present per unit volume of blood is also lowered; and if there is an outstanding diminution in the number of red blood cells, values for hemoglobin lower than normal are always obtained. The term *anemia* means in effect, therefore, a diminution in the total hemoglobin of the blood and in the number of red blood cells. Other pathological findings usually accompany these changes, but the term *anemia* does not include them, may not be applied to them.

There is some parallelism between fluctuations in disease of the total amount of hemoglobin and the

number of red blood cells, but the parallelism is very rough. This lack of close parallelism under different circumstances and in different conditions has been studied carefully and is of great help in differentiating various types of anemia and in determining the cause. If the hemoglobin is more than proportionally reduced as compared to the reduction in the number of red blood cells, each red blood cell will contain less than its normal quota of hemoglobin. The color-index will then be less than one. If, on the other hand, the red blood cells are more severely diminished than the total hemoglobin, each red blood cell will have more than its normal quota of hemoglobin. In an anemia of this type the color-index will be greater than one. This difference makes possible the first great classification of anemias into types.

1. Those with color-indices less than one
2. Those with color-indices greater than one

The first type of anemia, with a color-index less than one, may be said in general to be due, in large part, to some disturbance in hemoglobin metabolism; and the second type with a color-index greater than one primarily to disturbance in erythropoietic activity. In severe anemias where both disturbances are marked, the preponderance of one over the other indicates which process is the most active and permits us to speculate as to which is primary.

As soon as one attempts to classify anemias further than this, great difficulty is encountered. A true etiological classification is not available because the

etiology of many cases with anemia, of certain types of anemia, is not known. A common classification has been into (1) primary or idiopathic anemias, and (2) secondary anemias. This is obviously unsatisfactory because all anemias are probably secondary to some underlying cause, did we but know what it is, and a classification of clinical conditions based on the depth of our ignorance or the degree of our enlightenment in regard to them accomplishes no useful purpose. It is well within the limits of probability that exactly the same type of anemia for which at present no cause is known, may eventually be shown to result from several widely different causes. Of still more importance in making worse than useless the classification of anemias as primary and secondary, is a conception based on error entering into the early studies. This error is that the primary anemias only have a color-index greater than one, and the secondary anemias a color-index less than one. It is true that pernicious anemia, the etiology of which is unknown, has characteristically a color-index greater than one. But chlorosis, also of unknown etiology, has a very low color-index. And high color-indices are very commonly encountered in many conditions with anemia the cause of which may be readily demonstrated. Because of this error, in some quarters the term primary anemia has been used when the color-index was greater than one regardless of whether the anemia appeared to be idiopathic or dependent upon a readily demonstrable cause. And by the same token, a secondary anemia was one with a low color-index even

though of unknown etiology. As these terms are not permissible for use in describing the type of anemia, so should their use be heartily condemned to designate a clinical syndrome, as is sometimes done. The classification of anemias into primary and secondary is, therefore, not to be considered.

Ehrlich, on the basis of his early studies on the blood suggested a classification of anemias based on the regenerative forms that appear in the blood. The nucleated immature cells of the red blood cell series in the blood-forming organs from which the mature erythrocytes come in adult life are normoblastic in type. In embryonic life the bone-marrow shows fewer normoblasts and many megaloblasts, the embryonic precursors of the erythrocyte. In pathological conditions associated with anemia these nucleated immature red blood cells often appear in the peripheral circulation. Ehrlich's classification depended upon whether the nucleated red blood cells encountered were predominantly normoblastic or megaloblastic.

1. Anemias of post-embryonal blood formation type; normoblastic
2. Anemias of embryonal blood formation type; megaloblastic

This classification is worthy of mention from a historical point of view, but from no other. Either normoblasts or megaloblasts may be seen in the peripheral circulation in any type of anemia or in anemia in any condition. Whether the nucleated red blood cells in the peripheral circulation are principally normo-

blastic or megaloblastic depends, we believe now, upon the balance between the severity of the demand upon the blood-forming organs for new red blood cells and the ability of this tissue to respond. With healthy, normal blood-forming organs, the heaviest demand for erythrocytes probably does not result in the escape of many megaloblasts; and blood-forming organs with little reserve may throw out many megaloblasts even with minor stimuli to erythropoiesis. It is true that megaloblasts are more common in pernicious anemia than, for example, in an acute hemorrhagic anemia and in so far may help in diagnosis. This occurs probably, not because of some peculiar feature of the hemolytic anemia, but because the anemia is chronic and the ability of the blood-forming organs to produce erythrocytes is being exhausted. A patient with pernicious anemia in the early stages may have a normoblastic crisis with no megaloblasts present; and an acute hemorrhagic anemia in a patient already debilitated from some other cause may produce many megaloblasts. An observation as to whether the nucleated red blood cells present are principally normoblastic or megaloblastic in type, while an aid in prognosis, has little diagnostic import. It may not be used as a basis for classification of anemias.

The simple grouping of anemias used by Lazarus which could hardly be called a classification, is useful.

1. Simple anemias
    a. Acute post-hemorrhagic anemia
    b. The simple chronic anemia
    c. Chlorosis
2. Progressive pernicious anemia

This has the advantage that being extremely simple it contains no errors. Its disadvantage is that it is not sufficiently inclusive to cover the ground. Many anemias are encountered which cannot be placed in any of the groups. Naegeli attempting no classification, contents himself with indicating the conditions in which anemia is encountered and discussing the type of anemia found.

The classification of Morawitz has much to commend it. He divides anemias into two great groups.

1. Anemia due to blood loss or increased destruction of red blood cells
2. Anemia due to decreased blood formation

This classification does divide anemias into two great groups on the basis of their mechanism of production. It is of value because it focuses our attention on two methods by which anemia is induced. As a clinical classification it is not adequate because many of the anemias encountered in diseased states belong neither to one nor the other group, but to both. In the anemia of malignancy, for example, there may be chronic loss of blood and chronic blood destruction together with a functional depression of the erythropoietic tissue. The anemia in pernicious anemia is almost surely dependent upon the operation of both mechanisms. There is increased destruction of red blood cells in the body and probably, also, marked diminution in the power of the erythropoietic tissues to produce red blood cells. This classification on the basis of mechanism crosses that based on the type of anemia present. In anemias due to increased blood destruc-

tion or blood loss there may be a color-index greater or less than one; and in those due principally to inability of the blood-forming organs to produce cells either a high or a low color-index may be found.

In lieu of a satisfactory classification of anemias which is not possible, it might be wiser only to describe the nature of anemias and the mechanism of their production as far as known and to indicate the conditions in which the different types are found. All of this has already been suggested in the division of anemias into those with a high and those with a low color-index, and in the classification by Morawitz of anemias due to blood loss and to deficient formation.

Iron is an important constituent of hemoglobin and when there is a deficiency of iron, sufficient hemoglobin cannot be built up by the body. Iron metabolism is very slow. The body conserves jealously its supply of iron for when lost to the body it is replaced very slowly. The blood-forming organs can under stimulus produce red blood cells rapidly, much more rapidly than iron lost to the body can be replaced. Consequently when an anemia is due to hemorrhage, the red blood cells, replaced easily, are present in greater porportion relatively than the iron-containing hemoglobin. There is therefore a greater diminution of hemoglobin than of red blood cells, each red blood cell contains less than its normal quota of hemoglobin, and the anemia has a color-index of less than one. Such is the anemia due to acute hemorrhage or to chronic hemorrhage that is not of very long standing.

An anemia with low color-index not so far demonstrated to be due to loss of iron from the body as in hemorrhage is seen in chlorosis. Here there must be some disturbance of iron metabolism, the nature of which is not understood, to explain the great deficiency of hemoglobin seen in this condition. In chlorosis other unknown factors also are operative for there are certain definite qualitative changes in the red blood cells.

A chronic loss of blood in small amounts over long periods may, but usually does not, show the same blood picture encountered after acute hemorrhage or chronic hemorrhage of short duration. Under these conditions another factor comes into play for the color-index instead of being very low usually is near one and often is greater than one. It is practically always greater than one when the anemia is very severe. No satisfactory explanation of why this should be is available. Possibly the organism has time to adjust to the chronic loss of hemoglobin, the iron metabolism is speeded up, and there is not then the greater proportional diminution of hemoglobin as compared to red blood cells. It is fortunate that this occurs because the body can get along fairly well with very few red blood cells if the development of the anemia has been sufficiently slow, whereas a proportional, or more than proportional diminution of the hemoglobin at the same time would be fatal. As the severity of the anemia progresses there results a lowered functional activity of all the tissues including the blood-forming organs so that in these cases an

additional factor, that of deficient blood formation, is introduced. This further alters the blood picture from that seen in uncomplicated acute hemorrhage. If, as may occur under certain conditions such as some types of malignant disease, there is not only blood loss with eventually lowered hematopoietic activity, but also possibly some increased blood destruction in the body, all possible mechanisms in the production of the anemia are at work and it cannot be placed in any classification of anemias without introducing some error.

The anemia complicating acute infections may, in some instances, be caused largely by hemorrhage. In many this factor does not exist and inasmuch as an anemia with a color-index less than one may be encountered there must be some disturbance of hemoglobin formation, possibly due to inanition. The higher color-index often seen in acute infections, especially in the later stages of a prolonged one, can be explained by the lowered functional activity of the blood-forming organs in the presence of a normal or adjusted iron metabolism. No doubt, too, in some of these cases an increased blood destruction, a toxic hemolysis, comes into play.

These considerations illustrate a point which, because of a misconception apparently widely current, may perhaps merit special emphasis. A high color-index does not mean that the anemia is primarily a hemolytic anemia due to increased destruction of blood in the body as in pernicious anemia. It means only an anemia of long duration and slow development.

The explanation offered as to why this should be may need modification with increase in our knowledge about these things. Clinically, however, the fact is beyond dispute that a high color-index is not limited to anemias hemolytic in origin.

The anemia of inanition is possibly due to a lowered supply of iron and to lowered hematopoietic activity.

All the anemias so far discussed except that resulting from acute hemorrhage have been due to the operation of several factors, no one alone standing out predominantly. There is one great group of anemias in which, although more than one mechanism is at work in their production, one is especially prominent. In that great group of so-called hemolytic anemias, including pernicious anemia or Addison-Biermer anemia as its most important member, the most striking factor is increased destruction of blood in the body. In these cases there is rarely a color-index less than one because all the destruction of blood takes place in the body and the iron is conserved by it. Hematopoietic activity is also diminished in these anemias, probably because inhibited by the same hemolytic toxin which results in the increased destruction of blood.

Other anemias are encountered which are due apparently to an inhibition of hematopoietic activity alone, the so-called primary aplastic anemias. An aplastic stage of the blood-forming organs may occur in an anemia from any cause but the blood picture will show evidence of the mechanism of its production, the aplastic state being accompanied by, and

secondary to, other factors. The anemias designated as primary aplastic, however, while no doubt in part due to other factors, leave no uncertainty in one's mind that the main factor is a cessation of blood formation.

The blood pictures resulting from anemia in infants and young children differ from those in adults, and the relative frequency and importance of the different mechanisms inducing it vary. For example, hemolytic anemias are rare and when encountered seem to have been causing the child little or no inconvenience in most instances. Anemias of infancy are brought about, however, by the same mechanism as in adults; blood loss, blood destruction, disturbances of iron metabolism, and decreased hematopoietic activity.

In view of the points brought out above it will be seen that no satisfactory classification of anemias is possible and, therefore, none will be ventured. Anemias may, however, be conveniently grouped in the following order.

1. Anemias due primarily to blood loss
    a. Acute hemorrhage
    b. Chronic hemorrhage of short duration
2. Anemias due primarily to deficiency of iron
    a. Chlorosis
    b. Inanition
    c. Anemia of premature infants
3. Anemias due primarily to lowered hematopoietic activity
    a. Primary aplastic anemia
    b. Anemias associated with some hemolytic toxins
    c. Anemias often associated with acute myeloblastic leukemia

4. Anemias due primarily to blood loss, but also in part to lowered hematopoietic activity
   a. Repeated small hemorrhages over a long period
5. Anemias due primarily to increased blood destruction
   a. Pernicious anemia
   b. Hemolytic icterus
   c. Anemias associated with cirrhosis of the liver and spleen (?)
   d. Anemia of icterus neonatorum (?)
   e. Anemia of pregnancy (?)
   f. Anemia of some parasitic infestations
6. Anemia due to all three or any two of the factors: blood loss, increased blood destruction, and lowered hematopoietic activity
   a. Anemias of prolonged infections
   b. Anemias of some parasitic infestations
   c. Anemias of malignancy
   d. Anemias of pregnancy (?)

This listing of anemias according to the factors concerned in their production must, of course, be tentative. Those anemias about which there is great uncertainty as to their place in the list have been indicated by an interrogation point. Such a grouping probably contains some errors but is of value because, if one keeps in mind the possible mechanisms of production of anemia when examining the blood, more intelligent interpretation is possible.

Many of the anemias listed above are merely incidental to another condition present. Others designate a complete clinical syndrome and among these pernicious anemia is to be found.

The cases originally described as pernicious anemia were thought of and reported as idiopathic or essen-

tial anemias, in contradistinction to those anemias due to blood loss or other recognized cause. In addition to the anemia other findings were presented and from time to time additional special features have been demonstrated. With this increase in knowledge, it has become more and more evident that the different manifestations of this disease are not dependent on the anemia; that the anemia is but one disturbance among many presented by the patients. Furthermore, it has been shown frequently that any one or several of the special features encountered in pernicious anemia may be seen in other conditions. It should be emphasized that this is as true for the blood findings as for other features, for almost the same type of anemia may be encountered in syphilis, in malignancy, and in other conditions. A characteristic blood picture may not, therefore, be considered sufficient for a diagnosis of pernicious anemia, and the presence of such an anemia does not, in itself, constitute the disease. In addition it is most significant that among such cases there exist many features in common, more than between any one of them and any other cases with anemia placed elsewhere in the classification above. So although further studies will no doubt revise extensively this classification of anemias and may eliminate entirely pernicious anemia as a distinct clinical entity, and although one may deny that the anemia in pernicious anemia is primary or that it is the principal lesion upon which all the other pathological findings are based, one must at present recognize a distinct symptom complex which consti-

tutes a clinical entity. Pernicious anemia, Addison's anemia, and Addison-Biermer anemia are terms which, therefore, should not be used to indicate merely a certain type of blood picture. Their use must bring to mind an entire symptom complex, each feature of which is as important, if not so outstanding, as the anemia itself.

CHAPTER II

Occurrence

The prevalent opinion among physicians in general that the number of cases of pernicious anemia is increasing, is probably incorrect. Among the first 99,835 patients admitted to the Johns Hopkins Hospital from its opening until December 31, 1914, pernicious anemia was diagnosed 358 times, 0.0358 percent of all cases. Among the 60,786 patients admitted to the hospital from January 1, 1915 to December 31, 1922, pernicious anemia was diagnosed 220 times, 0.0362 percent of all cases. It is possible that in earlier days cases were diagnosed pernicious anemia which would not be included in this category now because the type of case diagnosed pernicious anemia has been drawn ever narrower, and this might tend to mask an actual increase in cases of true pernicious anemia. On the other hand, this would be offset to some extent by the fact that in recent years more cases of pernicious anemia are sent to the hospital than formerly because, first, physicians have cultivated the habit of treating medical, as well as surgical, cases in hospitals; and second, because blood transfusion, widely recognized as a method of treatment in pernicious anemia, is more conveniently carried out in hospital than at home. However this may be, pernicious anemia is not an uncommon disease and it is certain that any practicing physician will encounter a number of cases with puzzling types of anemia, some of which will be pernicious anemia.

Pernicious anemia practically never occurs in children. Among the first 36,000 non-surgical patients under fourteen years of age treated in the Harriet Lane Home for Crippled Children of the Johns Hopkins Hospital from its opening until 1922, not one case of pernicious anemia has been encountered. Doctor Howland in charge of the clinic states furthermore, that he has never seen a case of pernicious anemia in a child, thus enlarging upon the 36,000 patients seen by him in the hospital. Doctor Howland because of this vast number of cases studied without including one patient under fourteen years of age with pernicious anemia, is inclined to question the reported cases. He suggests that some may have been purpura or lymphoid leukemia. Various kinds of splenic anemia are common in children and occasionally a case is encountered which is difficult at first to differentiate from pernicious anemia. And in children unimportant disturbances may give rise to anemia showing most bizarre changes which are of no moment but which, if encountered in an adult, would be significant indeed. Such blood changes may confuse, but in a study of the urobilin excretion in a series of these cases by the method of Wilbur and Addis, Bass, Denzer and Herman did not find increased amounts in one case. Any case in the literature reported as pernicious anemia on the basis of the blood findings alone is, therefore, open to serious question.

Pernicious anemia undoubtedly occurs in the elderly but since several of the outstanding features of pernicious anemia are commonly found in the absence of the complete symptom complex in advanced age, the

diagnosis must, in these patients as in children, be accepted with reserve. General depression of functional activity, including hematopoietic function, may give rise to more or less anemia; and if this anemia is of long standing and slow development, the color-index may be high, even sometimes greater than one. Impaired kidney function may in a manner which has not yet been explained, be associated with some anemia. Disorders of the liver may cause anemia and some discoloration of the skin. The skin is commonly very sallow in the aged and if wrinkling is not pronounced may resemble the discoloration seen in pernicious anemia. Achylia also is often found in these patients. The common occurrence of malignancy, sometimes accompanied by a type of anemia almost indistinguishable from that of pernicious anemia, may further confuse.

Pernicious anemia, therefore, probably never seen in infancy or childhood, and of rare occurrence in old age, is a disease of adult life. The age incidence of 111 patients treated in the Johns Hopkins Hospital during the years of 1918 to 1922 inclusive, is as follows:

	Number of cases
0 to 10 years	0
10 to 20 years	1
20 to 30 years	3
30 to 40 years	17
40 to 50 years	26
50 to 60 years	37
60 to 70 years	18
70 to 80 years	9
80 to 90 years	0

It will be noticed that 56 percent of the cases are found in patients between the ages of forty and sixty years, 71 percent between the ages of thirty and sixty years. Only 13 patients, 11.7 percent, did not occur between thirty and seventy years. There were, as already pointed out, no patients under ten years, but one under twenty, and only 4 out of the 111 cases under thirty years of age.

The early reports of the Germans show many more cases of pernicious anemia among women than among men. This observation has not been confirmed by later English, Canadian and American students who found more cases among men than among women. The Germans probably were led into error because they did not draw the lines of diagnosis so sharply and included many cases of women with anemia associated with various phases of child-bearing. Osler in his text-book expressed the opinion that the disease is more common among men. Stengel also found the disease slightly more frequent in men than in women. In a series of 143 cases at the Peter Bent Brigham Hospital in Boston studied and reported by Levine and Ladd there were 59 men and 84 women. In a similar report by Willson and Evans of 111 cases of pernicious anemia studied and treated at the Johns Hopkins Hospital, Baltimore, during the years 1918 to 1922 inclusive, there were 82 men and 29 women. If the figures of these two reports are combined, there were out of 254 cases, 141 men and 113 women. Examination of all statistics leads one to the conclusion that the incidence of true pernicious anemia is about

the same in men and women, or possibly slightly more frequent in men.

Pernicious anemia is very uncommon among negroes. Only 9 of the 578 admissions for pernicious anemia at the Johns Hopkins Hospital from its opening until December 31, 1922, were in negroes, these 9 cases among 34,280 negro admissions during the same time. One of these patients, a female, was a characteristic case and ran the usual course. The others presented very mild cases, one of them regenerating his blood completely with no transfusions, and several others doing the same with but one. All these patients were mulattoes. The high incidence of syphilis among hospital patients of this race is interesting in this connection. Not infrequently an anemia resembling somewhat that seen in pernicious anemia is encountered in syphilis and this might, in the absence of a Wassermann test, lead to error. This anemia, however, improves rapidly under antisyphilitic treatment. For this reason, the diagnosis of pernicious anemia in negroes emphasizes two points: the blood picture alone, however characteristic of pernicious anemia, is not sufficient for a diagnosis; and pernicious anemia may never be diagnosed in the presence of a positive Wassermann test without most critical examination and only after a thorough course of antiluetic treatment.

Other racial considerations in regard to the occurrence of pernicious anemia are very difficult to determine. No completely satisfactory study of world distribution of the disease has been made; and because

of the different standards of diagnosis such a statistical study would not be of great value. Pernicious anemia appears, however, to be fairly common and of about equal frequency in all the big clinics of Europe and America. One most interesting and suggestive study of the occurrence of the disease in relation to race and nationality appears in the paper of Levine and Ladd. They compared first, the percentage of the total number of admissions to the Peter Bent Brigham Hospital of all patients from a given country with the percentage of the total number of pernicious anemia cases in persons born in that country; and second, the number of patients with pernicious anemia born in a given country to the total number of admissions to the hospital for all causes from that country. Although statistically definite conclusions from the figures here given are not warranted, the figures obtained are interesting and at least suggestive. Thus 9.4 percent of all medical admissions came from Russia, but only 2.1 percent of the cases of pernicious anemia were Russian immigrants. In contrast to this, 8.9 percent of all admissions came from Canada and 16.1 percent of the cases of pernicious anemia were Canadians. There were, covering the period of this report, 2193 Russians and 2070 Canadians admitted to the hospital, but among the Russians there were but 3 cases of pernicious anemia, while among the Canadians there were 23. The total number of admissions from these two countries is sufficiently large to give these statistics some value. The same discrepancy exists between the immigrants from Swe-

den and Italy. There were two and one-half times as many Italians as Swedes admitted, 668 from Italy and 278 from Sweden, yet there was but one Italian patient with pernicious anemia, whereas there were six Swedes. The Italians comprised 2.9 percent of all admissions with but 0.7 percent of all pernicious anemia cases; and the Swedes had 1.2 percent of total admissions to the hospital, and 4.2 percent of all cases with pernicious anemia. England, Ireland, Denmark and Germany may also be included with Canada and Sweden as producing a higher percentage of the total cases of pernicious anemia than of total admissions, with other countries tabulated just the opposite to this. The Russian figures are influenced by the fact that they include many Jewish patients thus giving the impression that pernicious anemia is uncommon among Jews. It would seem, therefore, that pernicious anemia is much more common among Americans, Canadians, English, Irish and Scandinavians than among people from Southern Europe. It appears also to be very uncommon in the tropics. Professor Oskar Klotz states that

> In Brazil I found that pernicious anemia was a very unusual disease. During a two and a half years residence in that country I made inquiries amongst quite a number of the doctors, and I found that the majority of them had never seen a case of true pernicious anemia. They did encounter many cases of grave secondary anemia, resulting from malaria, dysentery, intestinal parasites, tropical ulcers and other infections. These cases frequently presented many characteristics like pernicious anemia but in all of them it was not difficult to determine the cause. Dr. L. J. Lane of São Paulo, Brazil told me that he had seen three cases

which he believed were pernicious anemia, during a practice extending over twenty years. At least one of the cases occurred in an American who was a resident in Brazil for only a few years. One other case was brought to my attention, of an American who had gone to Ecuador and who after a severe attack of dysentery developed what appeared to be pernicious anemia. In a series of several hundred autopsies, I did not encounter a case of pernicious anemia on the post mortem table.

In general, therefore, I think it is correct to say that pernicious anemia is quite unusual in tropical Brazil.

This statement corresponds with the author's experience with somewhat more limited material in the Canal Zone, Panama.

Except for these special racial considerations, heredity has not been shown definitely to play a part in the occurrence of pernicious anemia. The writer has been able to demonstrate no familial tendency in any cases studied by him and nothing definite in regard to this could be gotten out of the histories of the 111 cases reported by Willson and Evans. In that series three brothers of one patient, one brother of two others, one sister of another, and the mother of one had died of some form of anemia. The mother of the last patient also had a cancer so the anemia there can readily be explained. There was no way of telling whether the anemia mentioned was pernicious anemia and in view of the frequency of other types of anemia, it seems likely that some cases were not. There were, then but five among the 111 patients who had had other members of their families die of some form of anemia. This percentage, 4.5, is not striking. In the series of patients reported by Levine and Ladd, however, 6.3

percent gave histories of pernicious anemia in the family. If these were, as the authors believed them to be, examples of true pernicious anemia, it certainly at least points to a family occurrence of the disease. Occasionally other reports suggesting the same thing (Decastello) appear; but still sufficient data are not available to permit one to state as a definite conclusion that there is a familial tendency to pernicious anemia. Indeed, it would seem that there is not.

There was tuberculosis reported in the families of 14 of the series of patients reported by Willson and Evans, or 12.6 percent. Two of these patients had more than one relative with tuberculosis and 12 had but one. In the families of 16, or 14.4 percent, cancer is recorded, one member being affected in 14, and two members in 2. Diseases of the kidney caused death in families of 8 of the cases, 7.2 percent. Heart trouble was mentioned in the family history of 35 patients, 31.5 percent.

Fifty-one of these patients gave family histories that did not include deaths from anemia, tuberculosis, cancer, kidney or heart trouble, and in which there was no record of metabolic or nervous disorders, or any blood disease. This suggests that, if the histories can be relied upon, pernicious anemia occurs with just about as much frequency in people coming from families in which there is no taint, as among those less fortunate.

No constant predisposing cause or causes can be demonstrated. Social circumstances and hygienic conditions of life seem to have no influence. The

occupations recorded in the histories of the cases reported by Willson and Evans include common laborers, stevedors, miners, carpenters, farmers, clerks, merchants, army officers, milliners, teachers, housewives, lawyers, ministers, physicians, ladies of leisure and retired capitalists. Just about as many and different occupations are mentioned as could reasonably be expected among any 111 people chosen at random. It would seem that occupation is not a factor in the causation of the disease and that it is just as likely to occur among those enjoying the better things of life as among others less fortunate who have little or no ease or luxury. Similarly, the history of these cases reveal no dissipation, or habit of eating, drinking, sleeping, working, sexual activity, or manner of life that would seem to have any importance in relation to the present illness.

Among the previous illnesses of the cases in this series, however, it was noticeable how frequently typhoid fever, pneumonia, and malaria was recorded. Thus, among these 111 patients, there were 24 who had had typhoid fever and pneumonia, 5 typhoid fever and malaria, and 1 patient had had all three. No other illnesses were recorded frequently enough to attract attention. It was noteworthy that none of the patients had had any cause for chronic blood loss or blood destruction.

CHAPTER III

Pathological Anatomy

When reading the literature on the pathological anatomy of pernicious anemia, one must examine very critically the diagnostic criteria used in the cases reported. Several clinical conditions may, unless care is exercised in diagnosis, be confused with true pernicious anemia; and inasmuch as most of the characteristic pathological changes may occur in other conditions, either singly or in groups, confusion may result. The complete collection of anatomical changes in pernicious anemia is, however, entirely characteristic of this disease. Some of the lesions found may be attributed to the anemia present, possibly because of the insufficient oxygenation; but others are wholly independent of this and are an integral part of the primary disordered condition constituting the disease.

The bodies of the patients are never emaciated, and are usually well nourished. A moderate edema of the face, dependent portions, and lower extremities is common. The subcutaneous fat is well preserved and presents a peculiar yellowish tint, nothing exactly like it being seen in any other condition. The skin shows a wholly characteristic discoloration, being grayish or dirty lemon color, entirely different from the simple pallor of anemia and cachexia, the gray pallor of malignant disease, the peculiar gray of Addi-

son's disease, and the yellow or brownish orange of icterus.

Minute ecchymoses, although not constant, are very frequently found throughout the body. They may be seen in the skin and mucous membranes, the peritoneal, pleural, pericardial, and meningeal surfaces, and in various organs of the body. Iron-containing pigment is also found widely distributed, this iron deposition being wholly independent of that found in concentrated areas due to minute hemorrhages. It has been suggested that this is due to therapeutic measures in which iron has been used, but this is incorrect for it occurs when iron has not been administered. This iron deposition, although widely distributed throughout the body, is found more abundantly in the liver, heart muscle, lungs, and cortex of the kidneys, and to a less extent in the spleen, lymph glands, bone-marrow and muscles. It may be demonstrated by immersing the tissues in a solution of ferrocyanide of potassium and weak hydrochloric acid, when they become a gray-blue color due to the development of Prussian blue. The iron pigment is most abundant in the liver. Its distribution is quite irregular, however, some cases showing an excess in one organ when it is greatly diminished or almost absent in the same organ of other cases.

The tongue, even at the autopsy table almost wholly devoid of white coating, is pale red, particularly at the edges. There is papillary atrophy in practically every case, in some mild and in many very marked. There may also be a distinct glossitis with furrowing and

open lesions, and small brownish patches marking the site of recent ecchymoses.

There is usually a marked pallor of the gastro-intestinal tract and brownish patches of ecchymoses are common throughout. Otherwise the stomach and intestinal mucosa and walls may be entirely normal. There is sometimes a glandular atrophy of the stomach and upper intestine with different grades of connective tissue infiltration, resulting in a rather smooth appearance of the mucus surfaces. This finding is encountered in other conditions than pernicious anemia, as is the associated achylia gastrica, and may not, therefore, be presented as a characteristic lesion of pernicious anemia. Because of the outstanding gastric symptoms in the disease the gastro-intestinal tract has been closely investigated. Thinning of the stomach and intestinal wall and degenerative processes of the mucosa, submucosa and muscularis; infiltration with lymphocytes, eosinophile cells, and other eosinophile bodies; degenerations of the nervous endings and nerve plexuses; and atrophy of the intestinal wall and structures of the intestine have been reported. All these findings should be listed as occasional occurrences and not presented as typical of the disease.

The heart presents rather constant findings. The organ is flabby and ecchymotic spots are commonly found over the epicardial and endocardial surfaces, and in the heart muscle itself. The fat around the heart is preserved and has the same yellowish tinge seen in the subcutaneous fat. The heart muscle is

pale and shows the streaking of fatty degeneration. Occasionally some slight dilatation may be demonstrated.

The lungs are pale, often show local edemas, and there are usually a number of ecchymotic spots. There may be an excess of pleural fluid, sometimes blood-tinged, but outstanding examples of this are very rare.

The kidneys and other structures of the urogenital tract are pale and may show ecchymoses. The kidneys themselves show evidence of fatty degeneration. Throughout the cortex in almost any locality iron pigment may be demonstrated, in some cases in slight amount and in others in relatively great abundance.

The liver is commonly of normal size, but may be slightly enlarged. Ecchymotic spots often dot the surface. The cut surface is ordinarily pale, but is not always so. Fatty degeneration is common. A fine, dust-like sprinkling of iron-containing pigment is the usual finding. This pigment is most abundant in the region of the fine bile canaliculi in the center of each strand of liver cells. A little pigment may occasionally be demonstrated in the endothelial macrophages—the Küppfer cells, capable of being vitally stained—and in the capillary endothelium. In these cells, however, it is as a rule very scant and to be found must be searched for diligently.

The spleen is sometimes quite markedly enlarged, is often slightly enlarged, but in a fair number of cases is of normal size. Occasionally the cut surfaces of the spleen appear more reddish than normal, but

in most instances no such abnormality is encountered. The splenic tissue is soft, and the malpighian corpuscles may be readily made out. More red blood cells than normal are to be found in the pulp between the venules, and many of these showing pronounced poikilocytosis, give a quite characteristic picture. One may see a few histogenous macrophages with engulfed red blood cells in all stages of degeneration, but these are not numerous. An occasional nest of immature myeloid cells is encountered, but in this particular the variation from normal, or from that encountered in several conditions associated with anemias other than pernicious anemia, is so slight that it cannot be emphasized as an important finding.

The lymph glands show practically no pathological changes. The hemolymph nodes may show some histogenous macrophages containing red blood cells as found in the spleen.

In the bone-marrow noteworthy changes occur. The type and extent of these changes vary tremendously. This probably is due in part to the great extent of tissue from which a specimen may be taken for examination. Normally, the marrow from the spongy bones is much more active than that from the long bones; and more cellular toward the end of the long bones than in the middle of the shaft. There are, however, real differences seen at autopsy in uncomplicated cases of pernicious anemia in bone-marrow taken from the same place, namely, the upper third of the femur. Sometimes this bone-marrow is cellular and at other times almost aplastic. The cellular

state is usually associated with evidence in the peripheral blood of hematopoietic activity, and the latter with an aplastic blood picture; but this is not always so. The variation in the pathological picture in the bone-marrow agrees very well with the clinical observations that the degree of anemia is, to some extent, independent of the severity of the disease. It is a forceful indication that the anemia is only a part of some underlying morbid condition, the blood being sometimes more and sometimes less severely attacked than other tissues of the body.

The bone-marrow from one of the long bones, in the gross appears gelatinous and of a reddish brown color, described by Cohnheim in 1876 as a raspberry-colored, jelly-like mass. Such bone-marrow contains the same histogenous macrophages engulfing degenerated red blood cells that are seen in the spleen and hemolymph nodes. There may be a fine deposition of iron-containing pigment among the reticular structures. Here and there a nest of hyperplastic myeloid tissue is encountered. By far the most characteristic change is the great number of megaloblastic cells. Normally there are very few megaloblasts seen in the bone-marrow of the long bones, practically all of the immature red blood cells being normoblasts. In pernicious anemia the megaloblasts are not only numerous but occur in nests. There may be an apparent lymphoid invasion, a relative increase in the number of lymphoid cells associated with a corresponding diminution in the myeloid and red cells. Under these conditions the preponderance of megaloblasts among

the red blood cells persists. There may be a very marked decrease in the number of red blood cells, the myeloid cells being usually at the same time proportionally diminished. The more severe the reduction in number of cells, the more immature, as a rule, they become. In such conditions practically none but megaloblasts may be seen, these so immature that they are very large, so-called gigantoblasts. The protoplasm of these cells stains very heavily with the basic stains, appears grayish-blue, or even true blue as the lymphocytes and is distinguished from them only by the irregularity of the protoplasm and the heavy chromation strands in the nucleus.

Changes in the nervous system are encountered in practically every case. They consist of a degeneration which affects the posterior columns, in most cases the posterior and lateral columns, but never the lateral column alone. The change is in the nature of a degeneration of the nerve tracts without any later shrinking of the cord, as in locomotor ataxia. These areas of degeneration, especially in the posterior columns, result in irregular secondary degenerations. The starting point for the rather widespread scleroses appears to be minute foci of degeneration in the region of the vessels. The blood vessels sometimes show hyaline changes, but are not regularly found diseased, though small hemorrhages are seen now and then. Characteristically the lesion is a scarring of the white matter of the cord with no involvement of the ventral gray column, of the dorsal gray column, or of the dorsal root ganglia. The extent of the lesion varies mark-

edly and in some of the more severe cases in which involvement of the nervous symptom is the predominant feature, there may be some degeneration and vacuolation in the gray matter of the cord. These findings are only in cases that progress very rapidly, however, and in them there is always some question as to the diagnosis. Exactly the same lesions are found in "subacute combined scleroses of the spinal cord," occurring with and without anemia, described by Dana, and by Batten and Collier, as a distinct clinical entity. It is still an open question whether this disease and pernicious anemia are not due to the same underlying cause, in one case the sheaths of the nerves, and in the other the envelopes of the red blood cells being principally involved. If they are the same disease, degenerations of the gray matter of the cord and brain should be included as an occasional finding in pernicious anemia. But when the symptoms are more those of pernicious anemia than of "subacute combined sclerosis of the spinal cord," that is, when involvement of the central nervous system does not precede the anemia, and when, throughout the course of the disease the anemia is the predominant symptom and the progress is not unduly rapid, the gray matter ordinarily escapes. The peripheral nerves usually are not injured although careful studies of these structures are conspicuous by their absence.

The muscular tissue is flabby and pale. Here one may see a deposition of iron-containing pigment both dependent upon and independent of minute hemorrhages, although such a finding is not common. There

is at times a fatty degeneration of the skeletal musculature. Mention has been made of a more pronounced fatty degeneration of the diaphragm, intercostal muscles and those of the eye.

The blood is pale and appears to be diminished in amount.

Except for those changes discussed with the clinical picture because they may be studied best under clinical conditions—changes in the blood, lesions of the optic disk, etc.—other structures in the body than those mentioned show no characteristic lesions. The deposition of iron-containing pigment can be satisfactorily explained by the increased destruction of red blood cells in the body. The histogenous macrophages encountered in the spleen, liver, lymph-glands and bone-marrow loaded with red blood cells merely indicate the presence of many deteriorated red blood cells in their vicinity. Anatomical changes in the gastro-intestinal tract are too inconstant and uncertain to merit consideration. The fatty degeneration of the musculature and parenchymatous viscera may be explained by the anemia alone. This probably is not the sole cause, however, for similar fatty changes do not necessarily accompany other chronic anemias. The foci of degeneration in the spinal cord cannot be explained by the anemia and no other lesion encountered can explain the anemia and megaloblastic change in the bone-marrow. The major, primary anatomical lesions in pernicious anemia, which cannot be explained with certainty by other lesions present are, therefore, fatty degeneration of many paren-

chymatous viscera and the muscles, the megaloblastic changes in the bone-marrow, the anemia, and the focal degenerations in the white matter of the spinal cord. All of these changes are probably due to the same underlying cause, possibly some hemolytic toxin, either foreign to or normally found in the body, or to some disturbance of lipoid metabolism such as discussed in the section on etiology.

CHAPTER IV

Etiology

The etiology of pernicious anemia is unknown. Many causes for it have been suggested, but none have been proved. Any discussion of this must deal then with speculations, with considerations of conditions somewhat similar from which interesting analogies may be drawn, or with observations and suggestions which, although interesting and suggestive, have not been carried far enough to permit definite conclusions.

Before one can appreciate the significance of the many promising observations and interesting suggestions put forward as to the basic etiology of pernicious anemia, one must recall the nature of the anemia seen in this condition. It is a so-called hemolytic anemia, an anemia due to an increased destruction of the red blood cells in the body. The red blood cells are destroyed more rapidly than they normally are, more rapidly than they can be replaced. This is proved by the increased amount of iron to be demonstrated in the liver and spleen, and by the work of Schneider and of Robertson who showed that in pernicious anemia there is a great increase in the amount of urobilin in the bile over that found under normal conditions. As presented by Addis the metabolism of the blood pigments probably is as follows. Hemoglobin from the worn-out red blood cells is converted in the liver to bilirubin. In the intestine the bilirubin

is reduced to urobilinogen which upon absorption into the blood becomes, through a process of oxidative polymerization, urobilin. The urobilin in the blood is carried to the liver and there converted into hemoglobin again. If this conception is correct, the amount of urobilin in the bile is a direct index of the amount of blood destruction going on in the body as maintained by Robertson and Schneider, and the increased urobilin in the bile as well as the almost constant presence of urobilin in the urine found in pernicious anemia can only mean increased blood destruction. Can this conception explain all the characteristics of the anemia encountered? Not entirely. The high color-index is that of any anemia, however caused, of slow development and long standing, and the presence of circulating immature forms, the nucleated red blood cells, can be accounted for by the urgent demand for red blood cells in the circulation made on already overtaxed hematopoietic organs. On the other hand, the irregularities in the size, shape, and staining reactions of the red blood cells, although possibly due to destructive forces acting on them in the circulating blood, are more likely the result of some noxious agent injuring them before they get into the general circulation. The persistent leucopenia and diminished number of platelets can most readily be explained by some agent exerting an inhibitory influence on hematopoietic function. The anemia in pernicious anemia, therefore, is probably due to an increased destruction of blood cells in the circulation or possibly elsewhere in the body, and probably also to an inhibition of hema-

topoietic function, perhaps by the same agent causing the pathological hemolysis.

Many conditions associated with a blood picture resembling slightly or closely that seen in pernicious anemia have been encountered and reported. The presence even of a wholly characteristic blood picture does not constitute the disease, and indeed, when another condition is found to account for the anemia, pernicious anemia also is probably not present. For this reason in examining the literature for suggestions as to the etiology of pernicious anemia, one must be careful to distinguish between studies investigating, or possibly merely describing, some conditions associated with a similar blood picture or contributing to it, and those attempting to search out basic disorders upon which the entire clinical syndrome might be based. In the literature there are many examples of the former type of study, these being of value in pointing out the several conditions other than pernicious anemia in which a somewhat similar anemia may occur. Most of these conditions are those causing an anemia of slow development and long standing, resulting in the later stages in more or less exhaustion of the hematopoietic function, either by chronic blood loss, by depression of hematopoietic activity, or by absorption of some known hemolytic agent in small amounts over long periods. Some of these conditions are: infection or tumor invasion of the bone marrow; some destructive processes involving the liver and spleen; prolonged fevers and wasting diseases such as phthisis, malignancy of various types, chronic nephri-

tis and syphilis with their associated depression of all vital functions; chronic blood loss as from esophageal varices, or gastric or duodenal ulcers, hemorrhoids, and some intestinal parasites; and the constant absorption into the system of some hemolytic agent as occurs in infestation with the fish tape-worm, *Dibothriocephalus latus* and possibly occasionally in intestinal stasis. Other conditions associated with an anemia resembling in type that seen in pernicious anemia and not to be explained by chronic depression of hematopoietic function, blood loss, or absorption of hemolytic agent are encountered; and inasmuch as in them the mechanism by which the anemia has been produced has not been explained, they are especially interesting to one searching for the true etiology of pernicious anemia. These conditions are: very rarely pregnancy, pyloric stenosis, and after gastrectomy; and very commonly sprue and combined, disseminated sclerosis of the central nervous system. However, the mere recording of these conditions and speculations as to the possible mechanism of production of the anemia found with them, while extraordinarily enlightening, has not pointed the way to a solution of the problem in question.

Among the first conditions described with blood pictures resembling that in true pernicious anemia, and sometimes confused with it, were some toxic disturbances of pregnancy, and infestation with the fish tape-worm, *Dibothriocephalus latus*. The mechanism of production of the former has not been explained and the studies so far carried out have yielded no sug-

gestions as to the possible etiological factor in pernicious anemia. Some suggestions have arisen from studies on the anemia sometimes associated with infestation with *Dibothriocephalus latus*. The production of the anemia by this parasite differs from that caused by most others in that it is not due primarily to loss of blood. It is caused by absorption into the body of a hemolytic agent from the worm. Faust and Tallquist isolated the hemolytic substance from the body of the worm and identified it as cholesterol oleate. This substance appears to act also as an inhibitor of hematopoietic function. The fact that only a few, possibly less than 20 percent, of the people harboring this parasite develop the anemia, and that the severity of the anemia seems to bear no relation to the duration of the infestation or the number of worms harbored, is confusing. Possibly the development of the anemia demands, in addition to the parasitic infestation, other contributing factors, or a susceptible individual. If this is so, then the etiology of pernicious anemia may be, by analogy, very complex, may be more than merely a hemolytic agent and hematopoietic poison. A very characteristic anemia has been produced by Schaumann and Tallquist, however, by salt solution extracts of the body of the worm and it has been suggested that only when worms or segments of worms die and are digested, that the lipoid is liberated and absorbed. This opinion is also expressed by Haden. Studies on *Dibothriocephalus latus* anemia are interesting in that they show that an anemia resembling in type that seen in pernicious

anemia may result from the action of a hemolytic agent and they at least raise the possibility that pernicious anemia may be due to an as yet undiscovered parasite. Indeed the clinical picture of pernicious anemia has much in it to suggest a parasitic invasion, rather a protozoon infection than otherwise. The chronicity, anemia, asthenia, fever, discoloration of the skin, enlargement of the liver and spleen, and the hopeless prognosis, all point in this direction.

Other observations suggesting a parasitic invasion as the cause of pernicious anemia are those on so-called pernicious anemia of horses encountered in central Europe. This disease is said to resemble pernicious anemia of mankind in many particulars and can be transmitted from one horse to another, or to a donkey, by injection of serum of an infected animal. The virus is very resistant to drying, but is thermolabile, being killed by heating for an hour at 58°C. The blood serum from human patients suffering from pernicious anemia injected into horses does not give rise to the disease in the animals. Seyderhelm claims to have found in the stomach of a large number of horses suffering from the disease, the larvae of several varieties of fly belonging to the *Oestridae* and to have extracted from the bodies of the larvae a toxic agent, not thermolabile, capable of setting up the disease. The blood of the horses with the disease thus artificially induced, he said, is capable of producing the disease in other animals, their blood in turn being infectious for yet others by reason of a thermolabile toxin as encountered in the original disease. Peters describes

a case of severe anemia of the aplastic type in a veterinary physician who had been treating horses affected with infectious anemia. One cubic centimeter of the blood of the patient killed a horse. Filtrates were also active. The disease started with diarrhea, alternating with constipation, occult bleeding and an exanthema. After two years the patient felt better but even after six years the number of leukocytes was only 1800 per cubic millimeter and the hemoglobin index was somewhat above normal. These findings, if confirmed, are very suggestive.

In a discussion of the possible etiology of pernicious anemia certain studies on sprue may not be passed without mention. This disease, with the changes in the tongue, the achylia gastrica and diarrhea, the nervous symptoms and the anemia simulating that in pernicious anemia so closely as to be practically indistinguishable from it at times, resembles pernicious anemia more closely than does any other. From the tongue and stools of patients with sprue, Bahr cultivated a yeast, *Monilia albicans*, and Ashford in Porto Rica isolated a yeast from the same source which he named *Monilia psilosis*. Smith reports the same results from the Philippine Islands. Since that time this same organism has been reported by others (Wood, Oliver, and Rogers) in cases of sprue, even in America. Ashford presents *Monilia psilosis* as a possible etiological factor in sprue in a convincing manner, when conditions in the intestine are, by reason of pancreatic insufficiency, rendered favorable for its colonization. Smith suggests that favorable con-

ditions for its implantation result from a diet deficient in vitamins. This same vitamine deficiency is suggested by Elders and van der Scheer. Can it be possible that pernicious anemia also is due to some such organism the implantation of which is made possible by some such disorder? Hunter was rather insistent that a streptococcic infection of the tongue and upper alimentary tract played an important part in the history of pernicious anemia. Hurst found *Streptococcus longus* in the duodenum in all patients with pernicious anemia and degeneration of the spinal cord, and in less than 11 percent of the controls. He believes that the achlorhydria allows toxic germs to pass to the duodenum. Marcora described a case of pernicious anemia from which at autopsy without previous infection a typhoid bacillus was recovered from the bone-marrow and spleen. Rahtjen reported an encapsulated diplobacillus from sputum of patients with anemia. Cornell presents *B. welchii* as the causative organism. These and other isolated reports like them are not convincing, and so far no organism, either previously known or newly discovered, has been reported from any long series of cases. If pernicious anemia is due to some organism or organisms, and such a possibility must certainly be considered, it is not known yet.

The anemia resulting from *Dibothriocephalus latus* infestation, that in horses possibly due to fly larvae in the stomach, and that associated with sprue suggest as the etiological factor of pernicious anemia a hemolytic poison absorbed from the intestinal tract. It has

been observed by Hunter that, since he found more iron in the liver than in the spleen in pernicious anemia, the hemolysis occurs in the portal rather than the general circulation, thus pointing to the absorption of a hemolytic poison from the intestinal tract. This suggestion is, however, open to many obvious criticisms. Another study also implicating the intestinal tract is that of Cederberg who, observing that animals dying in anaphylactic shock show a certain amount of hemolysis, believed that pernicious anemia is really a manifestation of anaphylaxis resulting from absorption from the bowel of foreign protein. This point of view is taken also by Faber who noted improvement in a few cases of pernicious anemia which were desensitized by injection of milk and other proteins. In the same connection the work of Iwao should be considered. Iwao produced in guinea-pigs an anemia closely resembling that of pernicious anemia by injection of p-oxy-phenyl-ethylamine. This in itself is not remarkable since there are other substances, notably soluble soaps, fatty acids, saponin, cobra-venom, toluylendiamin, etc., to mention only a few, which do the same thing. But p-oxy-phenyl-ethylamine or tyramin which has been isolated from putrefying meat, Swiss cheese and ergot can be produced from tyrosin by the action of various bacteria. One of these bacteria is the colon bacillus, so here we have demonstrated the powerful hemolytic activity of a substance which can be, and probably is not infrequently, produced in the intestine. Seyderhelm and Seyderhelm, Lehmann and Wichels suggest that such

putrefaction and absorption of toxic material results when the bacterial flora of the upper intestine becomes the same as that of the colon. They believe that here the colon bacillus is harmful whereas it is incapable of injury when confined to the colon.

The almost constant achylia gastrica found in pernicious anemia suggests that some anatomical or functional abnormality of or in the gastro-intestinal tract may be the primary cause. Atrophy of the gastric mucosa was noted early in pernicious anemia (Flint). This was considered the cause of the disorder by many observers who reported cases showing this (Fenwick, Kinnicutt, to mention only a few). Later it was realized that this organic lesion in itself, because of its frequent occurrence in other conditions having no anemia, could hardly be the sole underlying cause. Accordingly, it was thought that the disease might be due to some intoxication, the organic lesion of the gastro-intestinal tract being one manifestation of it, or that the achylia gastrica itself gave rise to disorders of digestion and absorption which might cause the entire clinical picture. The very frequent occurrence of achylia gastrica and its existence over many years in the absence of pernicious anemia gives sufficient answer to this suggestion. Accordingly the method of attack was changed and several students described extracts obtained in various ways from the gastro-intestinal tissues which have hemolytic properties. These results are not convincing because a hemolytic extract may be obtained from almost any tissue, even of patients never having had anemia. Of

really great interest in this connection is the patient reported by Hartman who, following complete gastrectomy for malignancy returned about a year later with a severe anemia resembling rather closely that of pernicious anemia. The case, however, lacked several features of the complete clinical picture of pernicious anemia. Hartman found in the literature a report of another such case studied by Moynihan. Meulengracht recently reported 5 cases diagnosed as pernicious anemia in which a stricture of the intestine was found. This observation is to be compared with the experimental work of Seyderhelm, Lehmann and Wichels who produced an anemia appearing to be hemolytic in dogs by making a stricture of the ileum about 5 to 10 cm. from the ileo-cecal valve. A possible explanation of the mechanism of the anemia in Meulengracht's cases is suggested by the observation of Seyderhelm et al. that the dogs developing anemia after this operation had a bacterial flora in the small intestines the same as that in the colon; and that in those dogs in which no anemia resulted, the bacterial flora was normal.

The interesting observations discussed above which might be expected to point the way to a solution of the problem of the etiology in pernicious anemia, have so far borne no fruit. The absorption of a hemolytic toxin either from some infecting organism or because of some abnormality in the gastro-intestinal tract, or a general infection, has not been proved. Nor has it been disproved, so any investigations in the future dealing with the etiology of pernicious

anemia must take under advisement all the points thus far raised even though they have yielded nothing in the hands of others.

Normally there is a constant destruction of worn-out, aged red blood cells in the body. Possibly the destruction of many red blood cells as occurs in pernicious anemia is no more than a pathological increase in the normal process. Did we but know how and where this process is carried out, it might lead to a solution of the mechanism of the anemia in pernicious anemia, and from there the basic etiological factor of this entire complex condition might be seen, for it seems reasonable to suppose that it is due to the same underlying disturbance causing the other pathological findings. The many possible ways in which red blood cells may be destroyed and disposed of in the body normally and under pathological conditions, which have been suggested and investigated, have led to no positive conclusions. However much these studies have added to our store of general knowledge, none has as yet helped toward a solution of the problem of the etiological factor in pernicious anemia, and they will not be presented here. This entire subject is admirably summarized and discussed by Rous.

It is certain that the spleen is a factor in destroying or removing worn-out red blood cells under normal conditions; and it is equally certain that in some manner it plays an important rôle in the pathology of pernicious anemia, and especially in hemolytic icterus. Robertson examined the blood in the splenic vein of normal animals and made a significant observation.

The red blood cells there showed a decreased resistance to hemolysis, the finding being definite as compared with red blood cells from the peripheral circulation of the same individual. Pearce and his collaborators noted that the resistance of the red blood cells of dogs to hemolysis by hypotonic salt solution, mechanical shaking, by hemolytic serum, and by saponin and cobra-venom, was increased after the removal of the spleen. These studies suggest that the spleen weakens the resistance of the red blood cells to hemolysis, and that this is a factor in the hemolytic anemias; that the hemolytic anemias are due to a hypersplenism. Heeres and Russchen observed many crenated erythrocytes in the blood from the splenic vein in human cadavers and dead animals. They believe that this indicates a hemolytic function of the spleen. This possibly does find application in hemolytic icterus where the cells are less resistant than normal, and great improvement sometimes with, but occasionally without increased resistance of the red blood cells, results from splenectomy. In pernicious anemia, however, it may not be an important factor for in this condition the red blood cells are more resistant to hemolysis by hypotonic salt solution than normal, and probably, although not surely, more resistant to chemical hemolysis; and clinical improvement does not constantly follow splenectomy. Eppinger attempted to correlate the anatomical changes which he found in the spleen in pernicious anemia with the increased hemolysis. He described a thickening and hyaline degeneration of the follicular

arterioles, thus reducing their lumen and apparently sidetracking a considerable portion of the blood stream entering through the central artery, diverting it from the sinuses and causing it to flood the cell columns of the pulp. Here were foci of myeloid cells and evidence of phagocytosis, but it seemed probable that there was not so much actual blood destruction as a sensitization of the red blood cells which rendered them more susceptible to hemolytic action on the way to the liver, in the liver, or elsewhere in the organism. The occurrence of remissions in this disease, however, during which the blood picture over several weeks often becomes greatly altered for the better makes it seem highly improbable that any organic injury giving rise to a more or less permanent lesion as Eppinger described, is the sole cause.

A mechanism by which the spleen may control, or participate in, the process of hemolysis has been presented by Eppinger and by King. These authors reported a decided increase in the iodin number, the degree of unsaturation of the fatty acids, of the blood in patients with hemolytic anemia and stated that there was some parallelism between the degree of unsaturation of the fatty acids and the amount of hemolysis encountered. Csonka also found an increase in the iodin number of the unsaturated fatty acids in anemia. Bloor reported an increased percentage and degree of unsaturation of the fatty acid in anemia produced by hemorrhage. This finding agrees very well with those of Faust and Tallquist who noted that oleic acid and its salts showed greater hemolytic

activity than stearic acid and its salts and were inclined to attribute this difference to the greater degree of unsaturation of the oleic acid; and with those of Lamar which indicated that the hemolytic power exhibited by a fatty acid or its soluble soap varied directly with its degree of unsaturation. Eppinger and King further observed that removal of the spleen lowered the degree of unsaturation of the fatty acids of the blood and resulted in an increase in the total fats and cholesterol. Bloor and McPherson also found the cholesterol in plasma increased after splenectomy. Inasmuch as cholesterol under some circumstances is a powerful antihemolytic agent, these observations are of real importance. The studies of these authors indicated, then, that upon removal of the spleen the amount of a well-known anti-hemolytic agent is increased, and changes in the highly hemolytic fatty acids and soaps resulted which they believed, on good authority, rendered them less hemolytic. Dubin and Pearce, however, did not find that the cholesterol was increased or fatty acids diminished in the blood of normal dogs after splenectomy. They did not report any studies on patients with hemolytic anemia and they varied the technique of Eppinger and King in some minor details, so their work in this connection is, as compared with that of Eppinger and King, more or less incomplete. Further questions in regard to the most interesting suggestions coming from the work of Eppinger and King are raised by the work of Clark and Evans and of McPhedran. Clark and Evans were unable to demonstrate in vitro any

antihemolytic power of cholesterol in ordinary solvents for hemolysis by sodium oleate; and, although this may have been because the cholesterol was not presented in the proper vehicle, it must be considered in this connection. McPhedran reported results contrary to those of Faust and Tallquist and of Lamar. He found that hemolysis by unsaturated fatty acids is not more active in proportion to the degree to which these acids are unsaturated, nor is it diminished when the unsaturated carbon atoms are saturated by halogens. On the other hand, McPhedran found that it is greatly diminished when they are converted into the corresponding hydroxyl acids which are hemolytic only to the same degree as the saturated acids. Furthermore, the idea that toxic hemolysis in disease results from the liberation of specially hemolytic fatty acids from the fatty complexes of disintegrating cells, is not supported by the findings of McPhedran. None of the fatty acids and still less any of the fatty complexes from which these acids could be obtained in any of the organs examined showed on analysis any evidence for the existence of fatty acids more toxic than the common oleic acid which is constantly being freed by hydrolysis from common fat in health.

The great amount of most suggestive work done in this field, far from clearing the problem of the etiology of the hemolytic anemias has rather resulted in confusion as to the way in which senile red blood cells are destroyed and disposed of, and the possible rôle of the spleen in hemolysis even under normal conditions. That the spleen in some normal manner, however, is

important in the hemolytic anemias is proved beyond question, but just what the part of the spleen may be and the mechanism of its action is still a mystery. No doubt several or many extra-splenic factors are involved. As Turk puts it, "The hemolytic diseases are the children, and the spleen is their mother, but the father is still unknown, and possibly there are several fathers."

Since the presence of no foreign hemolysin has been demonstrated in the hemolytic anemias, and an increase in the hemolytic activity of the hemolytic agents normally encountered in the blood is, to say the least, an unsettled question, a diminution of the antihemolytic power of the blood in these conditions is a possibility to be considered. Normally very powerful hemolytic agents in the form of soluble soaps are present in the blood, these probably not causing pathological hemolysis because of the antihemolytic power of the blood. If this were diminished in the hemolytic anemias, the hemolysis encountered could be accounted for. Clark and Evans investigated this point and found a marked diminution in the antihemolytic power of the serum in the hemolytic anemias and in conditions in which the liver and spleen are prominently involved in the disease process, the degree of reduction being roughly parallel to the severity of the disease. The amount of diminution of the antihemolytic power of the serum may only be an indirect measurement of the amount of some hemolysin present which has used up some of the antihemolytic substance of the serum. This may not be the case, however, and certainly the finding is significant,

especially in relation to the lowered cholesterol values in the same condition.

In spite of the fact that Clark and Evans were unable to demonstrate any antihemolytic property for cholesterol against sodium oleate in vitro, because of its antihemolytic properties under some conditions, cholesterol merits much attention in relation to the hemolytic anemias. Several very valuable studies have been carried out. The total amount of cholesterol in the blood of patients with pernicious anemia has been shown beyond question by Bloor and Knudson, by Denis, by Gorham and Myers and others to be lower than that in normal blood or that found constantly in blood from any other condition. Denis felt that the low cholesterol values in pernicious anemia bore no relation to the severity of the anemia; but Kipp noted a rough parallelism between these two features. This is of interest because Clark and Evans found fluctuations in the antihemolytic power of the serum to be more or less independent of the degree of the anemia, but parallel to the severity of the disease.

The investigations of cholesterol and unsaturated fatty acids go further in that the distribution of free cholesterol and cholesterol esters, and of fatty acids, in plasma and in the whole blood has been studied. Bodansky found that in normal dogs the cholesterol in the plasma was chiefly in the form of esters, ranging from 57 to 96.5 percent. In the whole blood that in the form of esters varied from 31 to 55 percent. He could find no cholesterol esters in the corpuscles, all that present under normal conditions being free or

loosely bound. When the dogs were rendered anemic by acetylphenylhydrazine, diisopropylhydrazine hydrochloride and toluylenediamine the amount of cholesterol in the plasma was diminished, this being almost entirely in the cholesterol esters. At the same time cholesterol esters could be found in the corpuscles. In the anemia thus induced the level of unsaturated fatty acids remained almost constant, but were increased in the corpuscles in the majority of instances. In the anemia following splenectomy no changes in the unsaturated fatty acid or cholesterol content of the blood was found except that cholesterol esters were more often found in the corpuscles. Some of this is contrary to the previous work of Eppinger, King and others, which has served as the basis for the doctrine of "hypersplenism" in certain hemolytic diseases. Bodansky stated that whenever the size of the corpuscles was increased without any hemoglobin increase, there was an increase in the unsaturated fatty acids and cholesterol esters. This was interpreted to mean that the red blood cells take an active part in lipoid metabolism and that in the presence of a diminished number of cells each assumes a larger burden of the work. In this connection might be mentioned Bloor's hypothesis that red blood cells take up fatty acids to join with lecithin and other lipoids. Gorham and Myers state that the reduction in total cholesterol seen in hemolytic anemias is largely in the plasma. Bloor and Knudson determined the ratio of total cholesterol in the whole blood and plasma and found it fairly constant in normal people. In

anemia they reported that this ratio is essentially the same. These findings are especially significant because only free (i.e., loosely bound) cholesterol may act as an antihemolytic agent. That in the plasma might act as an antihemolytic agent while that in the corpuscles by combining with hemolysin might be the very door through which the destructive agent enters. The free cholesterol in the plasma might act as an antibody and that in the cells as an activator to some normally present or foreign hemolytic agent (Ransom). Is it not possible that under normal conditions some hemolytic substances, possibly fatty acids, are held chiefly in the plasma as cholesterol esters, but that in anemia they are transferred, to some extent, to the free cholesterol in the corpuscles, this being just the process that destroys the least resistant cells? The studies of Flexner and Noguchi and of Kyes with cobra venom permit an interesting analogy to be drawn in this connection. Cobra venom when combined with lecithin forms cobra-lecithid, an active hemolytic poison. Hemolysis by cobra-lecithid is inhibited by cholesterol. Can it be possible that some normal or abnormal hemolysin in the body, blood or some organ, possibly the spleen, unites with the lecithin of the cells and thus destroys them when the available cholesterol in the plasma is lower than normal? It is suggestive, at least, to recall that the two tissues which contain more lecithin than any others in the body are the envelopes of the red blood cells and the sheaths of the nerves; and that the two outstanding features of pernicious anemia are a hemo-

lytic anemia and a diffuse sclerosis of the spinal cord. In this connection the spleen is again brought to the front by Kolmer who showed that the resistance of the red blood cells to cobra-venom hemolysis is increased after splenectomy in dogs. Inasmuch as the lysis of the erythrocytes is dependent upon the presence of certain lipoidal substances within the cells, Kolmer concludes that the spleen in some manner influences the lipoid content of the red blood cells. Thus, although no clear idea of the significance of these findings presents itself as yet, they seem to offer more promising possibilities than any heretofore discussed. The low values for cholesterol, an antihemolytic substance, especially in the plasma; the high degree of unsaturation of the fatty acids possibly present and which may mean increased hemolytic activity; the high fat fraction reported by Bloor and McPherson and Horiuchi possibly indicating the presence of abnormal amounts of hemolytic lipoids in the blood; and similar related studies, are extremely suggestive. These studies offer no certain evidence that abnormalities in the blood lipoids are responsible for the hemolytic anemias; but it is the author's firm conviction that if some such abnormality in the fat metabolism is not the sole cause of the condition, it will, when the final explanation is presented, be found to be a very important factor.

In view of the probable importance of the lipoids in hemolytic anemia, it is essential to determine, if possible, what factors may influence lipoid metabolism in pernicious anemia. Is it possible that the initial

lesion is one of the adrenal glands (Chauffard, Laroche and Grigaut)? This gland, especially the cortical portion contains a very high percentage of lipoids, sometimes as much as 20 percent of the fresh weight, occasionally up to 10 percent being cholesterol. They are so small that the total amount of cholesterol in them is less than that in the blood, central nervous system, or liver, so too much significance should not be attached to this fact. Grigaut, Rothschild, and Joelson and Shorr found an increase in the total cholesterol after unilateral or bilateral extirpation of the adrenal glands from dogs and rabbits, thus suggesting very strongly that they are in some way concerned in the regulation of cholesterol. Baumann and Holly repeated this work and arrived at other conclusions. When the animals survived the operation more than five weeks there was no increase in the amount of blood cholesterol during the first four weeks. It is of interest to note that in these animals the lipoid phosphorus values of the blood increased. Bauman and Holly found an increase in both the cholesterol and lipoid phosphorus during the last few days of life, but inasmuch as some of the animals had lived for four weeks after the double adrenalectomy without an increase in the blood cholesterol, this must be considered rather as a terminal event than as the result of the absence of the adrenal glands. This terminal rise of cholesterol explains the reason for the lack of agreement between the results of Grigaut, Rothschild, and Joelson and Shorr and those of Baumann and Holly. In no instance did the animals of

the earlier investigations live more than a few days, so it seems likely they were observing the premortal rise of cholesterol during all their period of observation. Sufficient work along these lines has not been done to permit definite conclusions and more is urgently indicated. One disorder of these organs, Addison's disease, has with pernicious anemia, two features in common; asthenia and a peculiar coloration of the skin. Alessandri reported a mobilization of cholesterol in the blood after injection of adrenalin.

Can the achylia seen constantly in pernicious anemia be the cause of a disturbance of lipoid metabolism, or itself a manifestation of some gastro-intestinal disturbance also giving rise to abnormalities in fat digestion and absorption? Few studies in this connection have been made, although possibly of so much promise; those having been reported only resulting in confusion as to the mechanism of digestion and absorption of fats and cholesterol under normal conditions. Mendel and Baumann found no absorption of neutral fats from the stomach of dogs and cats. Hirayama stated that the epithelium of the stomach does absorb fat. Of somewhat more interest in this connection are the studies of Mueller and of Knudson. Mueller found that, although the total cholesterol in the blood of dogs was increased after cholesterol feeding, the proportion of ester and free cholesterol was the same whether the cholesterol was fed as free or as ester. He presented evidence to show that esterification of the free cholesterol takes place in the lumen of the intestine, this being influenced by the presence

of pancreatic juice, and to a slight extent, by bile. On the other hand, Knudson found that after cholesterol feeding in dogs the increase in total cholesterol in the blood was entirely in the free cholesterol, and proportionally more in the plasma than in the corpuscles. Knudson suggested as an explanation of the discrepancy between his findings and those of Mueller that in Mueller's experiments fat was present and possibly some of the cholesterol fed was absorbed conjugated with fatty acids derived from that. If Knudson is correct, it would be extremely interesting to know whether cholesterol fed to patients with pernicious anemia, or simply with an achylia, would result in an increase in the total cholesterol in the plasma. Many other most pertinent questions present themselves upon which no work has been done.

Any discussion of the etiology of the hemolytic anemias tempts one to present in full all studies on the chemistry and physiology of cholesterol; and indeed, in such a discussion these studies would not be entirely irrelevant. Enough has been offered, however, to indicate the possible value of such studies and the great need for more knowledge on the subject.

Peabody and Broun quote earlier observers (Cohnheim, Osler and Gardner, Riess, Dickson, MacCallum) calling attention to the great amount of phagocytosis of red blood cells in pernicious anemia, and admirably emphasize the extent of this process by the reticuloendothelial cells of the bone-marrow. In view of these findings and since, as they correctly state, no chemical hemolysin has been demonstrated in the

hemolytic anemias, the possibility is suggested that this increased phagocytic activity is the cause of the anemia. This hypothesis does not offer any explanation of the sclerosis of the spinal cord as do those postulating a chemical hemolysin such as might well result from some disturbance of lipoid metabolism. And the qualitative changes in the red blood cells of the peripheral circulation make it appear more likely that the increased phagocytosis results from the great number of injured cells to be removed from the circulation.

In summary: We do not know that the etiological factor in pernicious anemia is not some organism, although none has so far been discovered. The anemias associated with sprue and with *Dibothriocephalus latus* infestation permit, by analogy, some such assumption; and there are some features of the disease which make it seem likely, especially a protozoan infection. Pointing in the same direction are the occasional isolated reports of organisms cultivated from patients dying with an anemia resembling that of pernicious anemia. We do not know that the disease is not due to the absorption from the gastro-intestinal tract of some hemolytic poison, although none has been demonstrated. Some studies on sensitization with products of intestinal putrefaction, and studies with such chemical hemolysins as tyramin no doubt occasionally formed in the intestine, bring this suggestion prominently to the front. We do not know that some functional or anatomical lesion of the gastro-intestinal tract is not the primary lesion; that the achylia gastrica does not result in some ab-

normality of digestion and absorption, possibly of the lipoids, upon which the disease is based. No conclusive information on this point is available but certain studies on the absorption of cholesterol from the upper alimentary canal permit speculation along these lines. We do not know the influence of the spleen in these conditions or even how it acts normally in regard to hemolysis. The anatomical change found in the spleen in pernicious anemia, the increased fragility of the cells in the splenic vein blood, and the decreased fragility of the red blood cells after removal of the spleen, make it the object of much interest in this connection. We do not know clearly what disturbance of lipoid metabolism is present, why it occurs, and what is its significance. The fact that cholesterol, an antihemolytic substance, is diminished in pernicious anemia, and especially that the free cholesterol in the plasma is diminished; that the total fats, possibly including some hemolytic lipoids are increased; and that the antihemolytic power of the serum is diminished in the face of the serum containing powerfully hemolytic fatty acids and soaps, open up many interesting hypotheses for investigation. In spite of all this obscurity and lack of certain knowledge, we do know that the spleen is prominently involved, and that there is some disturbance of lipoid metabolism. Whatever the basic etiology of this most complex disease may prove to be, when a clear interpretation of it is presented some disorder of splenic function will be an important factor, and the lipoids of the body will have much to do with it.

CHAPTER V

Clinical Description

Pernicious anemia is a complex clinical syndrome and has many characteristic features. It is, however, not always easily diagnosed. The manifestations presented by this most interesting disease may vary considerably, and several conditions may be encountered which resemble it very much, conditions in which a cause for the anemia may be demonstrated and which are based on etiological factors probably entirely different from those operative in pernicious anemia. The diagnosis of pernicious anemia does not rest on one feature alone, or on several features. All must be understood and considered if error is to be avoided.

SUBJECTIVE SYMPTOMS

By far the most disturbing symptom in patients with pernicious anemia is weakness and easy fatigability. This was mentioned in 79 percent of the 111 cases from the Johns Hopkins Hospital reported by Willson and Evans and was the chief complaint in 59 percent. When this symptom is pronounced the patients complain bitterly of a depressing feeling of weakness even when lying quietly in bed; or if up and about of an early appearing fatigue so complete that it makes any further effort almost impossible. The subjective feeling of weakness in those patients where it is very severe may even interfere with sleep. In other cases where

the symptom is not so marked the patients, while mentioning weakness, may recite a list of daily activities that belie their statement, indeed seem far beyond the work to be expected from a patient with an anemia of such severe grade. Weakness, therefore, although by far the most common symptom encountered and when present often of severe grade, may be very slight in some patients, and entirely absent in a few.

The next most common symptom in patients with pernicious anemia is one pointing to some disturbance of the digestive system. Such symptoms were mentioned by 59 percent of the patients studied by Willson and Evans and were the chief complaint in 29 percent. These symptoms were, in order of frequency,

Stomach trouble, dyspepsia and indigestion
Diarrhea
Nausea and vomiting
Anorexia
Sore mouth
Biliousness
Abdominal discomfort

This is essentially the same as in a series of 76 cases reported by Friedenwald and Morrison. The stomach disorders mentioned by the patients are usually, when explicit statements are brought out, very few in number. A feeling of epigastric discomfort is very common. Acute pain is practically never mentioned, the annoying feeling being one of pressure or of slight nausea. Occasionally the nausea is extreme and associated with vomiting. Anorexia is very common, much more com-

mon than the number of times it was mentioned by the patients above as the chief complaint would indicate. This is probably so because mere loss of appetite is usually taken as a matter of course by patients otherwise feeling badly. The anorexia manifests itself sometimes as just an indifference to food in general, sometimes as a definite repugnance to some special articles of food, and occasionally to a real aversion to any food at all. Meat is very commonly distasteful to these patients, as indeed might be expected in view of the constant achylia gastrica found in them.

Diarrhea, while fairly common and quite annoying, is by no means as commonly encountered as epigastric discomfort, nausea and anorexia. Diarrhea usually being due to the achylia gastrica in large part, is rarely mentioned by these patients in the absence of one of the above symptoms, and while it may be very protracted, is usually intermittent. It was present in 37 percent of the cases reported by Friedenwald and Morrison, and in 17 percent of the Johns Hopkins Hospital series.

Sore mouth is not one of the very frequent symptoms, being encountered in but 21 percent of the cases reported by Willson and Evans, but it is so very distressing when present that it forces itself on the attention. Any coarse or acid food causes in these patients a most intense burning of the tongue, gums, and mucous membranes, and sometimes of the esophagus. Adequate nourishment under these circumstances is extremely difficult to administer, these patients for quite good reason being very reluctant to eat.

Sensory disturbances of the extremities are common. Either tingling of the hands or feet, numbness of the hands or feet, or ataxia was mentioned as an annoying symptom by 24 percent of the patients from the Johns Hopkins Hospital. The nervous system was shown either by subjective symptoms or objective signs to be involved in 77 percent of these patients. The findings in this series concur well with other reports and with the clinical experience of all clinicians who have studied the disease closely. A numbness or area of anesthesia, a tingling sensation or formication in any one or all the extremities is very frequently mentioned, although the symptoms do not annoy greatly. Ataxia rather commonly, and partial or complete paralysis occasionally, occur. When weakness is an outstanding symptom, however, it is often very difficult to determine how much an inability to walk is due to this or to an ataxia rather than to paralysis, but difficulty in walking and in the finer movements of the hands are very frequently encountered. This sometimes amounts to an almost complete paralysis. Some doubt must be raised in regard to these cases, however, for although very rarely lesions of the spinal cord do progress so far that a spastic condition of the extremities amounting almost to a paralysis does occur, they are very rare in true pernicious anemia. Most of these cases are probably better classified with the "disseminated, combined sclerosis of the spinal cord" of Risien-Russell, Batten and Collier, and Dana. Those cases which, apparently having pernicious anemia, show a spastic paralysis quickly followed by a flaccid paralysis and loss of sphincter

control certainly belong to this group of cases whatever their relation to true pernicious anemia may be (see pages 41 and 81). Sometimes incoördination of the cranial motor nerves is encountered and some disturbance of the sensory nerves. Disturbance of vision is a really quite common symptom but in most instances it is due to retinal hemorrhages rather than to lesions of the central nervous system. Buzzing in the ears, no doubt due more often to the anemia than to nervous disorders, also is occasionally mentioned.

Not infrequently a nervous restlessness and sleeplessness is present and irritability is very common indeed. On the other hand these patients sometimes show apathy and weakness of application and will power. Such symptoms are probably in most instances wholly independent of any central nervous lesion. Cerebral lesions do occur, however, and are manifested by marked apathy, inattention to surrounding stimuli, loss of memory, disturbances of speech, and sometimes melancholia. Maniacal excitement, delirium and hallucinations have been reported, but they are very rare and are not of long duration. The coma commonly seen just before death probably is not dependent upon lesions of the cerebrum.

The outstanding symptoms of pernicious anemia are, therefore, weakness, some disturbance of the digestive system, and those due to lesions of the central nervous system, primarily sensory and especially prominent in the extremities. Not one of the series of 111 cases reported by Willson and Evans from the Johns Hopkins Hospital did not have at least one of these three major

disturbances, most of them had at least two, and many had all three.

Other symptoms very frequently met with are dyspnea, palpitations and precordial distress. These are usually brought on by undue activity and become negligible with rest in bed. The dyspnea and palpitations sometimes persist for several days or until a transfusion has been given but they are rarely of prolonged duration after treatment is instituted. Edema is another complaint heard but is not as frequently mentioned as its common occurrence would lead one to expect. This is probably because the other disturbances present cause so much more annoyance the edema is overlooked.

Headache is not uncommon. Dizziness is often mentioned, perhaps sometimes confused with ataxia. Pains in limbs and back are occasionally annoying. Very rarely loss of weight has been noticed. Some patients complain of their pallor.

PHYSICAL FINDINGS

Perhaps the most striking thing about patients with pernicious anemia is their appearance. They always have an unusual pallor, are not emaciated, show a slight puffiness under the eyelids which if they are severely ill may be quite marked, and have a worn, tired cast of countenance.

The discoloration of the skin, for it is a discoloration and not only an absence of color, is hard to describe. The skin has no touch of red and is of a grayish, pale lemon tinge seen characteristically in no other condi-

tion. It is always very delicate, never developing the outstanding lemon color of jaundice or the dirty gray of the later stages of malignancy. No real pigmentation in uncomplicated pernicious anemia ever occurs. Occasionally the skin is waxy. The mucous membranes are always pale, sometimes very markedly so. They do not frequently take part in the general discoloration of the skin, or perhaps more correctly speaking, they do take part but the tints developed are usually so delicate that they are not noticeable as they are in the skin. In the skin occasionally, and in the mucous membranes more frequently, small purplish red spots of petechial hemorrhages are seen.

Patients with uncomplicated pernicious anemia are not emaciated. Some few lose a little weight, but in no case is this extreme. Indeed this very point is a helpful diagnostic observation. It is very common to see a patient very ill, worn, and pale, yet well nourished instead of cachectic as one would expect if the general appearance were due to anything else. Furthermore, this good state of nourishment continues until the end, those patients who lose a little weight being in the early stages as often as in the later. Others die without having lost any weight worthy of note. Occasionally patients with pernicious anemia gain weight for short periods during the course of the disease. This is sometimes a sign of improved condition but more often the reverse. A gain in weight frequently is due to an increasing edema dependent upon a failing circulation and diminished kidney function (Christian) and possibly also in part to deficient oxygenation of tissues.

A worn, tired, more or less resigned facial expression in these patients is very common. It contrasts markedly with the dullness of expression in the acute infections, the anxiety of the dyspneic, the distress and apprehension of those in pain, the cheerful optimism often in the face of the tuberculous. This impression is heightened when the hair is gray or white as it is likely to be in patients at the age at which pernicious anemia is common. Levine and Ladd give figures to show that gray hair is more common in patients ill with pernicious anemia than it is among others and that it is frequently soft and silken.

The eyes in addition to having the occasional conjunctival petechiae mentioned above show retinal hemorrhages rather frequently. Among 77 patients who had ophthalmoscopic examinations in the series of cases from the Johns Hopkins Hospital, it was recorded as absolutely normal in 8. In 53 of the patients minor abnormalities were mentioned. The remaining 16 showed retinal hemorrhages, in one eye alone in 6 cases, and in both eyes in 10 cases. Rather severe hemorrhages were noted in 2 of these latter. The hemorrhages may be anywhere in the retina but are more common in the vicinity of the disk than elsewhere. Sometimes they are so large that vision is seriously interfered with. Their frequency and extent increase with the severity of the disease and are therefore a greater factor in the late stages than earlier. Those coming early in the disease usually clear up. The minor abnormalities of the optic disk very commonly noted are a pallor of the disk, some dilatation of the vessels, and edema of

the nerve head and retina especially in the region of fresh hemorrhages.

The findings in the mouth are of interest. The tongue is always quite clean and less pale at the edges than in the center. A coated tongue and a diagnosis of pernicious anemia is a combination to excite suspicion. Furthermore, a papillary atrophy is very frequent. It is encountered in some degree in about half the early cases and is severe in a few. In the later stages it is marked in many cases and present to some extent in most. Sometimes the tongue is deeply furrowed, even ulcerated, this giving rise to the soreness complained of so bitterly by a good number of pernicious anemia patients. The gums are frequently swollen and in spite of the anemia often somewhat reddened. A furrowing of the mucous membranes elsewhere in the mouth is an occasional finding.

The condition of the teeth in pernicious anemia has excited some interest as a source of the etiological agent. Teeth in bad condition and pyorrhea of course are found. Good teeth and healthy gums are also seen in many of these patients so any abnormality in this region has probably no relation to the disease in question.

The ears, nose, throat, sinuses and antra show no abnormality characteristic of pernicious anemia. The same applies to the thyroid gland, lymph nodes of the neck, and the chest.

The heart may be entirely normal and usually is. A hemic murmur over the precordial area and over the great vessels is an occasional finding. In a few cases

in the later stages some dilatation of the heart may be demonstrated. The pulse is usually slightly accelerated but is not always so, especially in the patients who are confined to bed and who are improving. Pernicious anemia does not influence the blood pressure in most cases, any variations from normal encountered being dependent upon something else. In a few cases a systolic blood pressure lower than normal is recorded which one feels is due to the asthenic state associated with the disease. The pulse pressure, the form and regularity of the pulse, and the quality of the arteries are not influenced by the disease.

The abdominal wall shows no abnormality characteristic of the disease. It is noteworthy that the panniculus is well preserved.

The spleen may be enlarged but is not so in most cases. In the series of cases reported from the Johns Hopkins Hospital it was not palpable at any time during their stay in the hospital in 80 percent of the patients. Among these it was enlarged to percussion in 5 percent, thus leaving 75 percent of the cases in which enlargement of the spleen could not be demonstrated by either percussion or palpation. The spleen was palpable only at the costal margin in most of the remaining 20 percent, but in some it was larger, in one patient extending a hand's breadth below.

Enlargement of the liver is possibly slightly more common than splenomegaly. In the series of cases mentioned above it was found in 33 percent. In most of these it was not extensive but in a goodly number the

liver extended 3 cm. below the costal margin, and in a few 4, 5, and even 6 cm. below.

In the author's experience the presence, absence, or extent of the splenomegaly and hepatomegaly seem to bear no relation to the stage or severity of the disease. This in general may be said about their relation to each other. Many cases have some enlargement of the spleen with no enlargement of the liver, and many in which no splenomegaly may be demonstrated show some enlargement of the liver. If either the spleen or liver is markedly enlarged, however, the other usually shows some enlargement, and occasionally to approximately the same extent. Minot and Lee say that those cases having enlarged spleens are likely to show more hemolysis, less evidence of myelotoxic activity, run a relatively slow course and have less striking remissions, and show greater benefit following splenectomy. They point out that these patients resemble acquired hemolytic jaundice more closely than other cases.

The genitalia and rectum show no changes characteristic of the disease. The extremities show no changes except edema. Edema of the face and lower extremities is very common, and of the hands and buttocks somewhat less so. It usually clears up very satisfactorily with rest in bed in those cases which improve. In those not improving it may not clear up entirely. Edema is very commonly found in patients, therefore, when they first appear for treatment and when in the later stages of the disease.

The physical findings in reference to the nervous system vary tremendously. The most common prob-

ably is some disturbance of the reflexes. They may be increased, may be unequal on the two sides, may be diminished, or entirely absent in the legs or arms, or both. The abdominal and cremasteric reflexes are less frequently affected. Paresthesias, particularly of the lower extremities, are very common. Ataxia with loss of the finer movements is of somewhat less frequent occurrence than the foregoing but is fairly common. These cases resemble tabes dorsalis very much. While often not severe, very few patients with pernicious anemia do not at one time or another show some evidence of involvement of the spinal cord. In the series of cases reported from the Johns Hopkins Hospital, 54 percent had disturbance of sensation, and 70 percent abnormality of the reflexes. In these 8 percent showed a positive Babinski sign. Sometimes a spastic paralysis sets in and this may go on to a flaccid paralysis with loss of sphincter control and very great disturbance of sensation. These cases always progress very rapidly. Sometimes in them the involvement of the blood is not very pronounced so that they go to exitus without the severity of anemia one might ordinarily expect. They may very rarely show extreme wasting, have lancinating pains, have marked disturbance of sensation with dissociation of pain, touch and temperature perception, and have girdle sensations. In a word, in the occasional case the lesion progresses so extensively that the findings duplicate those in syringomyelia and are to be differentiated from this only by the history and blood findings. The great question of classification in regard to such cases has already been

raised. Whether they should be classed with pernicious anemia or with the "disseminated combined sclerosis of the spinal cord" studied by Risien-Russell, Batten and Collier and by Dana is difficult to decide.

The cases with most marked involvement have subjective symptoms, objective signs and easily demonstrable lesions of the spinal cord. In the milder cases, however, no constant relationship between these factors can be demonstrated. One not infrequently sees a patient with marked subjective symptoms—formication, tingling, weakness—in the extremities and no demonstrable disturbance of objective sensation or of the reflexes. Sometimes, although more rarely, marked objective signs are present when little or nothing has been said about subjective symptoms. Occasionally, with pronounced signs and symptoms, a very minor lesion in the cord is found; and sometimes rather widespread cord lesions result in very little annoyance to the patient.

Involvement of cerebral areas in addition to the spinal cord must be expected. Such cases must be very rare, however, and only a few cases are reported. In studying a case suspected of having involvement of the higher areas, one must be careful not to be misled by disturbance in the special senses because of peripheral lesions and in the psyche because of the anemia and discomfort alone.

Involvement of the peripheral nerves seems not to occur. Those few reports purporting to describe such cases which may be found do not bear critical examination. One must remember in the face of a suspected

neuritis that arsenic, a common therapeutic agent in pernicious anemia, is capable of inciting just that lesion.

BLOOD LIPOIDS

In the section on etiology certain evidences of disturbance of lipoid metabolism have been mentioned. The most outstanding finding has been the diminution of the total cholesterol in the whole blood as shown by Bloor and Knudson and Gorham and Myers. The total amount of cholesterol in the whole blood found by Bloor in 5 normal men and 6 normal women varied from 177 to 208 mgm. per 100 cc. blood, giving an average of 190.7 mgm. The average of that which was in the form of ester was 33.6 percent. With this are to be compared the findings in pernicious anemia. The blood of 3 patients had 156, 156, 166 mgm. of cholesterol per 100 cc. of blood, an average of 159.3 mgm. The average of that in the form of ester in these cases was 39.1 percent. In the plasma alone somewhat different figures were obtained. The total cholesterol in the plasma of 17 normal men and 9 normal women varied from 140 to 221 mgm. per 100 cc. of blood, giving an average of 203.5 mgm. The average of that in the form of ester was 58.6 percent. The plasma of 9 patients with pernicious anemia showed total cholesterol from 140 to 170 mgm. per 100 cc. of blood, with an average of 156.4 mgm. That as ester varied from 44.2 to 70 percent, with an average of 60.7. These figures indicate that the reduction of cholesterol in pernicious anemia is principally in the plasma, an observation supported by the work of

Gorham and Myers. According to Kipp the amount of diminution of the cholesterol is roughly parallel to the severity of the disease. This is not in accord with the findings of Denis. Denis further noted that there was an increase of both lecithin and cholesterin in the whole blood and plasma of pernicious anemia patients after splenectomy.

METABOLISM IN PERNICIOUS ANEMIA

Von Noorden in 1894 was the first to study accurately the metabolism in pernicious anemia. He was unable to show what was then thought to be the case, that protein decomposition was increased. He even found a retention of nitrogen in some cases and quoted others (von Stejskal and Eben, Strauss, Bloch) who had done the same. With the rapid destruction of red blood cells taking place this finding was surprising. It invited one to think, as suggested by Mohr, that it was dependent upon the recovery under treatment of cases previously subjected to a period of underfeeding. Rosenquist found cases of pernicious anemia in which periods of increased nitrogen excretion alternated with periods of nitrogen retention. In regard to all these findings von Noorden and Umber suggested that in anemia irregularities of the functional activities of the alimentary canal and of the kidney might well explain irregularities of excretion of nitrogen and account for temporary variations in the amount of nitrogen excretion if pathological deviations were not too great. Mohr, however, agreed with Rosenquist but stated that the irregularities were independent of hemoglobin

findings, being due rather to other variable factors such as the intensity of action of some toxic agent which might be operative. This observation is supported by some of Rosenquist's work which showed that in the anemia due to *Bothriocephalus latus* in which Tallquist had brought evidence of a toxic action, there was loss of nitrogen dependent upon the presence of the worm in the body which changed to a nitrogen retention after removal of the worm. Von Noorden quoted Bohland and Vannini as having made a similar observation in patients with anemia due to *Anchylostoma duodenale.*

In more recent times this same subject has been investigated by Peters and Rubnitz and by Gettler and Lindeman. One feels more confidence in these results because of improved methods of investigation. Gettler and Lindeman found the non-protein nitrogen, urea, and creatinin values of the blood somewhat higher than normal and the uric acid and the amino-acid content much increased. These investigators also found the blood sugar to be abnormally high and the alkaline reserve below normal. The specific gravity of the blood was found astonishingly low. Peters and Rubnitz reported a marked decrease in the total solids and total nitrogen of the blood in not only the blood of patients with pernicious anemia but also in all other anemias which they investigated. The total plasma nitrogen, in contradistinction to the total blood nitrogen, either remained within normal limits or increased in percentage above that in most normal bloods. These observers stated that the levels of whole

blood nitrogen in the anemias were the essential chemical correlates of the number of red blood cells because there was a striking proportionality in these two independently determinable factors. The decrease in specific gravity of the blood, in the total solids, and in the total nitrogen would seem therefore, to be dependent solely on the decrease in the cellular elements of the blood. In view of this, Peters and Rubnitz make the further suggestion that since in all severe anemic conditions the whole blood nitrogen decreases while the plasma nitrogen tends to increase, the resultant ratio of the first to the second constitutes a sort of nitrogen index. Changes in this index, from the direction of variation in both factors, may be used to indicate the state and progress of the anemic condition. The value of this ratio tends to diminish in proportion to the severity of the anemia.

From what has been presented above one might expect that an increased excretion of nitrogen in the urine would be a more or less common finding in pernicious anemia. This supposition is supported by two modern investigations, by Minot, and by Pepper and Austin, who found it in cases studied before and after splenectomy. This loss of nitrogen was converted into a nitrogen retention by splenectomy in the cases of both these observers. Mosenthal easily accomplished the same result in cases to which he fed high protein diets.

An increase in the bile salts of the plasma has been observed in anemias by Blankenhorn, this increase being much more marked in pernicious anemia than

in any other condition. Blankenhorn suggested that this may be due to lowered kidney function. He recorded the observation that the severity of the nervous lesions clinically seemed to stand in direct relation to the amount of bile salts present in the plasma.

Meulengracht and Iverson studied the blood sugar in pernicious anemia with 260 determinations on 17 patients. Occasionally they found an increase in the fasting blood sugar and sometimes a prolonged and possibly also steeper blood sugar curve. These variations were independent of the degree of anemia.

Renal function in pernicious anemia is impaired, the degree of impairment running more or less parallel with the severity of the anemia. This has been shown by Christian who carried out the Mosenthal modification of the Hedinger and Schlayer test meal for kidney function on 14 cases of pernicious anemia. The data given indicate that in severe anemia renal function is disturbed in much the same way as in patients with advanced chronic nephritis. Among Christian's patients there were both the young and the elderly. In the older patients the influence of arteriosclerosis and degenerative changes in the kidneys could not be ruled out but in all but one there was no evidence of these conditions. In the young patients there was no reason to expect it. It seems more probable that the disturbance of kidney function found is the result of the anemia or of the underlying disturbance causing the disease, either a nutritional or toxic disturbance in renal cellular activity. Stieglitz attributes these findings to the accumulation of iron in the convoluted

tubules. This and the changes in function he feels are so specific that the condition might be called the nephritis of pernicious anemia. These findings are of interest in connection with the points brought out in the preceding paragraphs. Since kidney function is apparently so markedly impaired the early investigations of the nitrogen excretion in the urine may be of little value. It also suggests that the increased values for non-protein nitrogen, urea, creatinin and uric acid reported by Gettler and Lindeman are dependent solely on the disturbance of renal function rather than upon any inherent quality of the disease process.

URINE ANALYSIS

Pathological findings in the urine of patients with pernicious anemia are very common. Albumen occurs in more than half the cases, rarely in excessive, but usually in appreciable, amounts. Casts are not of very frequent occurrence. When they are found they are dependent upon some concurrent condition, not upon pernicious anemia, and their number and kind are influenced by the same consideration. Urobilin is also a very common finding, being demonstrable in the urine of about half the patients who are studied carefully over any period of time. This is to be expected because the presence of urobilin in pathologically demonstrable amounts in the urine results from increased blood destruction. When urobilin tests are positive in the specimen of one day it is usually so repeatedly even in the face of an improving blood picture. Urobilin is more frequently found in those cases

which are in bad condition and which do not react promptly and extensively to treatment. Acetone is found in the urine in a few cases on single examinations. It is rarely present repeatedly. Blood and hemoglobin may be present in the urine in great amounts after a transfusion if the blood of donor and recipient have not been matched properly, or if because of repeated transfusions, the patient has developed antibodies for any blood. In addition to this, blood occasionally appears in the urine in small amounts as a result, no doubt, of petechial hemorrhages in the kidneys as occur elsewhere in the body. The urine analyses on the cases in the Johns Hopkins Hospital studied by Willson and Evans contained albumen in 55 percent, casts in 19 percent, urobilin in 50 percent, acetone in one specimen in 6 percent, bile in 2 percent, blood in 2 percent. Sugar and diacetic acid were not encountered.

GASTRIC ANALYSIS

The findings on analysis of the gastric contents of patients with pernicious anemia are very interesting and very important. Free hydrochloric acid is almost always absent; indeed as far as the author's experience goes it is always so. Free hydrochloric acid was not found present in any analysis of the gastric contents on the series of 111 cases reported from the Johns Hopkins Hospital. Among the series of 107 patients in the Peter Bent Brigham Hospital, Boston, reported by Levine and Ladd, free hydrochloric acid was found but three times. In one case, it was present in an appreciable amount. In another it was absent on three

analysis, the fourth showing but 6 percent acidity. The third case was one in which the diagnosis of pernicious anemia was by no means established. Among these 218 carefully studied cases, therefore, there was but one sure case showing an appreciable amount of free hydrochloric acid in the gastric contents. In a series of 57 cases reported by Friedenwald and Morrison figures not so striking as the above were obtained. There was an achylia gastrica in 42 of these patients, free hydrochloric acid between 5 and 12 percent acidity in 11 patients, and normal amounts in 4 patients. In spite of an occasional report like this there are quite a number of careful clinical observers who state that absence of free hydrochloric acid in the stomach contents is as constant a finding in pernicious anemia as is the anemia itself. Whether this be true or not, certainly it is so common that a diagnosis of pernicious anemia in the presence of free hydrochloric acid is one to be questioned. Similarly, the total acidity is low, although complete achylia is not present in the majority of cases. Lactic acid is an occasional finding, 3 percent of the Johns Hopkins Hospital cases. The microscopic examinations are of no interest.

DUODENAL CONTENTS

The duodenal contents regularly show an increased amount of urobilin over the normal. The amount found varies considerably, being in general greater when the patient is sickest and when the anemia is most severe. According to Robertson and Schneider the amount of increase over the normal of urobilin in

the duodenal contents may be used as an index of blood destruction. This seems entirely reasonable when one recalls the cycle of blood pigment metabolism worked by Addis (see page 44). Hansmann and Howard measuring the amount of urobilin in the urine and stool stated that by variations in these values, prognosis as to improvement or decline in the condition of the blood could be made.

STOOL

As in the urine and duodenal contents, so in the stool increased amounts of urobilin and urobilinogen are encountered. Quantitative measurements of that in the stool are not of so much value as those made on the duodenal contents because of the inconstant amount of absorption of urobilin from the intestine into the blood. (The same factor is one among several which influence the amount excreted in the urine making deductions from quantitative determinations here somewhat uncertain.) In about 20 percent of the cases positive tests for bile are obtained. Other than the increase in urobilin and the occasional finding of bile no other abnormality appears regularly on stool examination. Its value is chiefly in proving the absence of pathological findings characteristic of other conditions that are sometimes difficult to differentiate from pernicious anemia. Occasionally a little blood is present on one analysis. If this is present constantly the diagnosis of pernicious anemia should be questioned until the source of the blood is determined. By the same tokens, if any parasites or parasitic ova appear,

pernicious anemia should not be kept as a final diagnosis until the disease has persisted after the intestinal parasites have been removed and time has been allowed for recovery from the effects of the infestation. The finding of an abnormally large, frothy, acid stool with diminished pancreatic ferments should suggest sprue instead of pernicious anemia.

WASSERMANN TEST

Positive Wassermann tests are not infrequently found in patients suspected of having pernicious anemia. Since, however, cases of syphilis sometimes show an anemia resembling that in pernicious anemia very closely, many of these patients prove not to have pernicious anemia and are entirely cured by antiluetic treatment. Some cases with true pernicious anemia do give positive Wassermann tests and in these antiluetic treatment results in only temporary improvement. Such cases are infrequent, however, so that it can be said that patients with pernicious anemia rarely have positive Wassermann tests. Among 141 cases reported from the Peter Bent Brigham Hospital, Boston, above referred to, there were but 6 with positive Wassermanns, 4.3 percent. The incidence of positive Wassermann tests for all medical admissions to this hospital is 12 percent, so in pernicious anemia it is well below the average. Among the 111 cases reported from the Johns Hopkins Hospital, Baltimore, there were but 2 cases with positive Wassermann tests.

TEMPERATURE

After transfusions some elevation of temperature is

most common, usually very slight, but sometimes going to high levels. Very frequently there is a high fever in these patients just before death. Wholly aside from fever thus caused, patients with pernicious anemia are subject to minor fluctuations in temperature during the course of their disease. Long periods with normal temperature alternate with those in which slight degrees of fever are seen each day, perhaps all day. Among the patients reported from the Johns Hopkins Hospital, there were 29.7 percent who had fever with no demonstrable cause other than the pernicious anemia. The fever in these patients varied irregularly between normal and 100°F., occasionally going as high as 101, but rarely above this. Patients with fever from time to time do not, as a rule, feel as well as those without it. This is the only difference between patients with fever and with normal temperatures, those with fever apparently progressing as well and improving as much as those without it. Just what feature of the disease or variation in its manifestations causes the fever has not been determined.

BLOOD

Changes in the blood in pernicious anemia constitute, probably, the most outstanding features of this disease. An anemia is regularly present, the only finding that is without question always encountered in all stages of the disease. The total volume of blood is not always diminished but Denny has shown that it very frequently is. He observed that the plasma volume is usually normal, the diminished volume of the whole blood being

due to the decrease in cell mass resulting from the lowered number of cells present. In a few cases in which the total blood volume is not less than normal in spite of a diminished cells mass, it is due to an increased volume of plasma. In view of these observations one would expect the blood to look thinner than normal and it does. When the skin is punctured the drop of blood obtained looks watery. It flows freely and for a longer time than normal. Clotting time, as well as bleeding time, is prolonged.

The anemia present consists of a diminution in the number of cellular elements and in the amount of hemoglobin. Since it is a hemolytic anemia, and especially since it is an anemia of long standing and slow development, the number of red blood cells is proportionally less than the amount of hemoglobin. Put another way, the decrease in number of red blood cells is greater than in the amount of hemoglobin. Each red blood cell contains more than its normal quota of hemoglobin and the color-index is, therefore, high. This is the first point to be made and emphasized in regard to the blood picture of pernicious anemia. A high color-index is obtained in any anemia that is of long standing and slow development when it has become severe. If the anemia in conditions other than pernicious anemia is of moderate severity, the color-index is more commonly not very high; and if the anemia is slight, it surely is not. In pernicious anemia, however, the color-index is high, usually more than one, even when the anemia is of mild degree. Accordingly, when one sees a patient with slight anemia

showing a high color-index, pernicious anemia should be carefully considered. If, however, the patient has a severe anemia, the finding of a high color-index is very little help in making a diagnosis of pernicious anemia. In pernicious anemia the elevation of the color-index above normal values tends to vary more or less with the degree of anemia. When the anemia is mild, the color-index approaches normal; when the anemia is severe, it is higher. Thus, although a patient with a mild anemia and a high color-index does have, in all probability pernicious anemia, a mild anemia with a color-index of practically normal value does not mean that pernicious anemia is not present. Color-indices that are not above normal in pernicious anemia are, however, very rare, and low ones are never obtained. Among the 111 patients reported from the Johns Hopkins Hospital, there were but 7.2 percent on admission and 10 percent on discharge who did not show color-indices greater than the upper limit of normal. When the anemia is severe, very high color-indices are the rule. In the series of cases just mentioned one of 1.7, another of 1.6, and four of 1.5, are recorded.

If in the blood of pernicious anemia there is more hemoglobin in proportion to the number of red blood cells than normal and each cell contains more than its proportion of hemoglobin, one would expect to see them appear darker than the normal cells. They frequently do. Often, however, even in the most severe cases of pernicious anemia a blood film is examined in which the cells appear lighter than normal in spite of a high

color-index. This can only mean that the red blood cells are larger than normal, the increase in size over the normal being greater than the increase in hemoglobin content. In other words, although the cell carries an increased amout of hemoglobin, because of its increase in size there is proportionally less hemoglobin in it and it appears lighter than normal. This explanation is supported by the investigations of Capps and Haden who found the cells in pernicious anemia increased in size, the increased volume index of Capps. Haden goes so far as to say that this increased volume index is constant in pernicious anemia and is one of the most important diagnostic features. He further derives what he designates the "saturation index" which is in effect the proportion of hemoglobin to the volume of the red blood cells. He finds this rarely greater than one in pernicious anemia. When it is greater than one the cells would, of course, appear darker than normal; when less than one, they would be paler. Pijper describes a new method of determining the size of red blood cells in pernicious anemia. An ordinary blood film can be used as a diffraction grating. When a beam of parallel rays of white light strikes a diffraction grating at right angles, and a positive lens is placed at the back of the grating, a series of spectrums will appear on a screen placed at the back of the lens at its focal distance. The size of the spectrums is a function of the size of the elements of the grating. A blood film used as a grating produces circular concentric spectrums, and their size is an expression of the average diameter of the red blood cells constituting the grating.

The formula, which on physical grounds applies in such cases is:

$$d = \frac{l\sqrt{4f^2 + D^2}}{D}$$

in which d is the diameter of the blood cells, D the diameter of the colored circle in the spectrum of which l is the corresponding wave length, and f the focal distance of the lens used. Twice the value of l must be substituted if the second spectrum is used for measuring purposes instead of the first. From the formula d can be calculated from D. It is not claimed that a blood film forms a perfect diffraction grating, but for practical purposes it is suitable. Csaki reports studies showing that the size of the red blood cells in pernicious anemia vary directly with the amount of hemoglobin. This point needs further study.

The next observation to make in regard to the anemia in pernicious anemia is that it persists. Once the disease has manifested itself sufficiently to bring the patient to a physician, the anemia demonstrated, while varying in degree, never disappears even after the most successful period of treatment. Included in the series of patients from the Johns Hopkins Hospital there were those who had just begun to feel badly and had reported to the hospital very early, there were many who responded excellently to treatment with extensive and prompt remissions, and some who when discharged from the hospital looked like normal folks and felt the same. Yet in all the red blood cell counts done on these 111 patients not one of five million is recorded,

and only 2 of four and one-half million. These last counts were obtained on patients just before discharge from the hospital, one in a man and one in a woman. Eleven of these patients when discharged had red blood cell counts between four and four and one-half million, making only a total of 13 patients, 11.7 per-cent, who when discharged after treatment did not have red blood cell counts lower than four million.

The anemia in pernicious anemia is characteristically very severe. In the same series of cases, 60 percent had red blood cell counts under two million on admission; and 87 percent under three million. There is certainly no other condition commonly associated with anemia in which such severe grades of anemia are so constant.

The qualitative changes in the red blood cells are the next most striking feature. Each one to be mentioned is seen in other conditions, but with one or two exceptions much more infrequently and in most instances not in so pronounced degrees. Most qualitative changes in the red blood cells only appear in other anemias when the anemia is moderately severe, and in them when most severe, they are not frequently as outspoken as in even the milder stages of pernicious anemia.

Variations in size of red blood cells, anisocytosis, and irregularities in form, poikilocytosis, are present in every blood-film examined from patients with pernicious anemia. The grades of anisocytosis and poikilocytosis vary to some extent independently of each other, but each is more marked when the anemia is

severe than when it is of milder degree. In the more pronounced grades of anemia usually both, but always one of these features is striking. If only one is very marked, it is poikilocytosis in far the majority of cases. If, in the presence of a severe anemia, anisocytosis and poikilocytosis are not frankly present, the condition is surely not pernicious anemia. When the anisocytosis is marked the cells with regular contour may vary in diameter from 4 to 14 microns with practically no neighboring cells of the same size. In the presence of marked poikilocytosis the variation in size may be even greater, for then small microcytes no more than two microns in diameter are present. Anisocytosis is much more common in secondary anemias than poikilocytosis, and in them is often seen alone. Poikilocytosis occurring much less frequently in anemias other than pernicious anemia, is practically never seen in the absence of anisocytosis. The irregularities in shape may in milder cases consist of merely some elongation of a few cells, some bending, or a few points projecting. When severe the irregularities are very bizarre. Red blood cells shaped like arrow-heads, crescents, hammers, etc. are to be seen. The picture when anisocytosis and poikilocytosis are pronounced is very striking, and immediately suggests pernicious anemia.

Irregularities in staining reactions, polychromasia, in contradistinction to aniscocytosis and poikilocytosis which can be seen as readily upon examination of a fresh preparation as a stained film, can only be made out after the blood has been stained. Certain variations in color of the red blood cells in the stained film

are dependent upon the different amounts of hemoglobin in them. This is pronounced in pernicious anemia. With Romanowski stains cells with very much hemoglobin in them appear dark copper color, the ones with normal or less than normal, various shades of buff or lemon yellow. The chief variation in color of the red blood cells is due, however, to the basophilia. This is by no means so common in pernicious anemia as anisocytosis and poikilocytosis. Very many blood films from patients with all grades of anemia show no basophilia at all. When present it is almost always diffuse basophilia. Punctuate basophilia is very rare. Diffuse basophilia is most common during periods of regeneration. When it does occur it is seen in all types of cells, but possibly more frequently in large regular cells than in small, distorted poikilocytes. Basophilia, however, is not common enough, or if present not pronounced enough in pernicious anemia to be a helpful diagnositic feature. Indeed it is the author's opinion that basophilia is more often encountered in certain secondary anemias than in the anemia associated with pernicious anemia.

Nucleated red blood cells are commonly present. They usually are found in small or moderate numbers, the heavy showers of them constituting normoblastic crises being of rare occurrence in pernicious anemia. When these showers of nucleated red blood cells do occur they mean that the patient is not in the later stages of the disease and the prognosis for the immediate future is good. All forms of immature red blood cells are encountered from the most immature

gigantoblasts and megaloblasts through intermediate forms to almost mature red blood cells of normal size and shape and containing or extruding very small dark nuclei. Nucleated red blood cells certainly occur most frequently in those cases which improve the most during the period of observation. They are, therefore, of some prognostic help. The presence of normoblastic red blood cells usually means that improvement has begun. On the contrary, if the nucleated red cells are predominantly or entirely megaloblastic the indication is not favorable, but rather the reverse. This may mean that the hematopoietic organs are hard pushed, that not only can they not supply the demand for mature red cells, but that they cannot even produce slightly immature ones and must fall back on very early forms. Except for this special observation, their presence or absence does not bear any relation to the stage of the disease or its severity. They can occur or not in more severely ill patients, or in those but mildly ill. In the Johns Hopkins Hospital one patient admitted with 1,344,000 red blood cells and 28 percent hemoglobin and discharged with 2,088,000 red blood cells and 40 percent hemoglobin showed nucleated red blood cells in moderate numbers in each of five blood films examined. Another patient admitted with 1,184,000 red blood cells and 21 percent hemoglobin and discharged with 2,488,000 red blood cells and 46 percent hemoglobin had no nucleated red blood cells in five films examined. Among the less severe cases, one patient admitted with 3,230,000 red blood cells and 49 percent hemoglobin and discharged with 4,144,000

red blood cells and 60 percent hemoglobin had nucleated red blood cells in six of nine blood films examined. Another admitted with 3,290,000 red blood cells and 65 percent hemoglobin and discharged with 3,370,000 red blood cells and 75 percent hemoglobin had no nucleated red blood cells in eight films examined. There is some evidence that young megaloblastic forms with reticulated nuclei are more common in pernicious anemia than in other conditions. Piney classified many nucleated red blood cells from cases of pernicious anemia and other conditions and arrived at this conclusion. If this is true, the presence of megaloblasts is an aid to diagnosis. It probably is true in most instances, but in the author's opinion, is not pronounced enough or sufficiently constant to be given much weight in making a diagnosis of pernicious anemia.

Reticulation of the red blood cells is not remarkable in pernicious anemia. In some cases there is no increase above normal, in many there is a slight increase in number, and in a few cases a rather marked increase to perhaps 15 percent may be found at times. In relatively few cases are the higher percentages of reticulated red blood cells, 20 percent and above, found. When they are numerous it is a temporary condition. High counts are never maintained as in hemolytic icterus. MacLachlan in studying the variations in numbers of reticulated red blood cells in pernicious anemia found they had some prognostic significance. Increased counts were one of the earliest changes in the blood in an impending remission, particularly during the course of a series of transfusions, while absence

of an increased count, or a diminished count under these conditions usually indicated that a remission was not likely to appear. Locke and Hackman studying the reticulated red blood cells in pernicious anemia found that there was a greater percentage of them in the lower than in the higher dilutions of hypotonic salt solutions, while just the reverse held for the reticulated cells in acquired hemolytic jaundice. From this the authors concluded that those in pernicious anemia were biologically less hardy than those in other conditions.

One of the most outstanding features of the blood picture in pernicious anemia is a leucopenia. The average of the highest white blood cell counts recorded at any time on each of the 111 patients in the series from the Johns Hopkins Hospital is 7,363. This is the more remarkable because it includes counts on patients when they had a transient leucocytosis associated with infection, as follows:

	Number of cases
Between 20 and 21,000	1
Between 20 and 19,000	1
Between 17 and 18,000	1
Between 14 and 15,000	3
Between 13 and 14,000	1
Between 12 and 13,000	5
Between 11 and 12,000	3

The average of the lowest white blood cell counts recorded on all patients is 3,058. This in itself is striking enough, but when one studies those patients who, at one time or another, had a higher count it is shown that practically all of them had a leucopenia at one time in the hospital. There were only 11 patients out of the

entire group who did not have at one time or another less than 5,000 white blood cells; there were but 6 who; always had more than 6,000; 3 never fell below 7,000 but none maintained a white blood cell count of 8,000 or above during his stay in the hospital. Very low counts may be expected. Indeed a patient with anemia and even a mild leucocytosis, in the absence of an infection, probably does not have pernicious anemia. If there is a leucocytosis associated with a very severe anemia, he certainly does not.

The differential white blood cell formula in pernicious anemia is interesting. The polymorphonuclear neutrophile cells are diminished, the average percent in all the counts on all the patients of the Johns Hopkins Hospital series being 55.8. The average number of polymorphonuclear neutrophile cells found in the differential counts made was below 65 percent in 74.8 percent of these patients. It was below 60 percent in 61.3 percent of them. In only 10 patients out of the 111 was the average of the polymorphonuclear neutrophile cells over 70 percent, and in 8 of these, counts are included which were made during leucocytosis of severe infections. A good percentage of polymorphonuclear neutrophile cells can occur in pernicious anemia for there was one differential count showing a polymorphonuclear neutrophile percentage of over 70 in 50 percent of the same patients. Accordingly, although a polymorphonuclear neutrophile leucopenia is a characteristic feature of pernicious anemia, if an increased percentage of polymorphonuclear neutrophile cells is found in one count it does not preclude the possibility

of this diagnosis. A sustained polymorphonuclear neutrophile leucocytosis, however, especially in the absence of a demonstrable infection, does make it quite unlikely. Variations in the total number of polymorphonuclear neutrophile cells are important in prognosis. When they are increasing it is a favorable sign. When they are decreasing it means that a remission is not to be expected.

Eosinophilia is not a characteristic feature of pernicious anemia. The average number of eosinophiles found in all the differential white blood cell counts done on all the patients in the Johns Hopkins Hospital series was 1.58 percent. Among them, however, there were several very high counts recorded; one each of 17 percent, 16.7 percent, 15 percent, 14 percent, 12 percent, and 10.5 percent and 2 each of 13 percent, 10 percent, 9.2 percent and 9 percent. These single counts, of course, bring up the averages and make even more striking the low figures given above for them. These statistics compare very well with the findings in the cases from the Peter Bent Brigham Hospital, Boston, of Levine and Ladd and show that although at times, really very many eosinophiles may be present is pernicious anemia, they are for the most part not increased and eosinophilia is not a characteristic feature of the disease. It has been suggested that when the eosinophile count is high it indicated a mild stage of the disease and an early and marked remission might be expected. This is not supported by the findings in the Johns Hopkins Hospital cases. Indeed, nothing in these cases could be found to account for the eosino-

philia, and it was not constantly associated with any other feature so that any diagnostic or prognostic import could be attributed to it. The eosinophilia in these cases appeared to be independent of even the total white blood cell count and the percentage of polymorphonuclear neutrophiles.

The number of large mononuclear (not lymphocytes) and transitional cells is essentially normal. The average of those found in all the counts on all the above cases was 5.2 percent. There were 4 patients with an average of these cells which was quite high—between 14 and 16 percent, but only 5 others, or 9 in all, 8.1 percent, with more than 9 percent of these cells. Apparently, therefore, in regard to these cells as eosinophiles, one may say that, although high counts may occur, they are not characteristic.

Immature white blood cells may be encountered occasionally in the peripheral blood of patients with pernicious anemia. Myelocytes were seen at one time or another in 38, or 35.1 percent of the series of patients under discussion. They were seen more than once in 22 of these patients, four or five times in 9. Usually there were only a few but in several cases 5 percent were recorded, in a few 6 percent, in one 8 percent, and in another 10 percent. Immature lymphoid forms, pathological lymphocytes, were seen in 12 cases, 10 percent. The highest number of these cells recorded was 6 percent, and in but one of the 12 cases were they observed in more than one blood film.

Observations on the blood platelets constitute a very important feature of the blood picture in pernicious

anemia. They are never increased in number. Even those cases from the Johns Hopkins Hospital mentioned above which had a leucocytosis associated with an infection showed only what might be considered a low normal count. Under ordinary circumstances, they are sometimes diminished but slightly. More often the diminution is marked. The number of platelets seen varies directly more or less with the degree of anemia present. When the anemia is severe they may be almost absent. One may search many fields of a blood film before finding one. When found it is often small and poorly stained. In stages where the anemia is slight platelets are still small in size and reduced in number. In this respect pernicious anemia differs markedly from anemias due to hemorrhage and some other non-hemolytic anemias. In anemia of hemorrhage, although the white blood cells may not be increased, the platelets usually are. For this reason a note as to the number of blood platelets is very important in deciding whether a given blood film shows a picture characteristic of pernicious anemia.

CHAPTER VI

Diagnosis

The diagnosis of pernicious anemia is not difficult in most instances. Usually it may be strongly suspected from the history and physical examination alone, and largely confirmed upon examination of the blood and urine. Some cases are encountered, however, which present difficulties, and inasmuch as there are other conditions which may resemble pernicious anemia closely at times, it is essential that these be examined carefully. Furthermore, it is important to limit the diagnosis of pernicious anemia to a definite clinical syndrome and not spread it over a variety of conditions in which a similar, or almost similar, blood picture is seen. For these reasons all available data should be collected and considered before a diagnosis is ventured; it should not be made on the blood picture alone, or on any other single feature.

In times past when a blood picture showed an anemia with high color-index, some poikilocytosis and anisocytosis and the presence of an occasional nucleated red blood cell, a diagnosis of pernicious anemia was made. Now we know that these features are of very common occurrence and are frequently seen in conditions which afford an explanation for the anemia and are based on etiological factors quite distinct from those probably operative in producing the complex clinical condition to which the term pernicious anemia is now

limited. As already pointed out a high color-index means only a long standing anemia of slow development; and the presence of qualitative changes such as anisocytosis, poikilocytosis and polychromasia are by no means limited to the hemolytic anemias. Nucleated red blood cells, even megaloblasts, are seen in many other conditions and truly are more numerous in certain types of regeneration from hemorrhagic anemia and leukemia than in pernicious anemia. Diverse forms of nucleated red blood cells are most commonly seen in the anemias of childhood and pernicious anemia is very rare in young patients. Indeed pernicious anemia may be said never to occur in childhood and anyone making such a diagnosis in a patient under fourteen years of age must realize that he is probably in error and must hold it tentatively while searching for further explanations of the anemia. Other features of pernicious anemia than those of the blood picture may also be seen in other conditions. The peculiar color of the skin may be readily confused with that seen in other diseases. The slight enlargement of the spleen is very common. A mild intermittent fever is often encountered. An achylia gastrica is of frequent occurrence. An increase in urobilin in the urine is commonly found. And symptoms of scleroses in the spinal cord are seen in several conditions other than pernicious anemia. Rarely is the characteristic combination of these features, although they often occur singly or in pairs, encountered in conditions other than pernicious anemia. Even in the presence of the most typical clinical picture, however, a diagnosis of pernicious anemia should

not be made until all other causes for chronic anemia, and all known parasitic invasions have been ruled out.

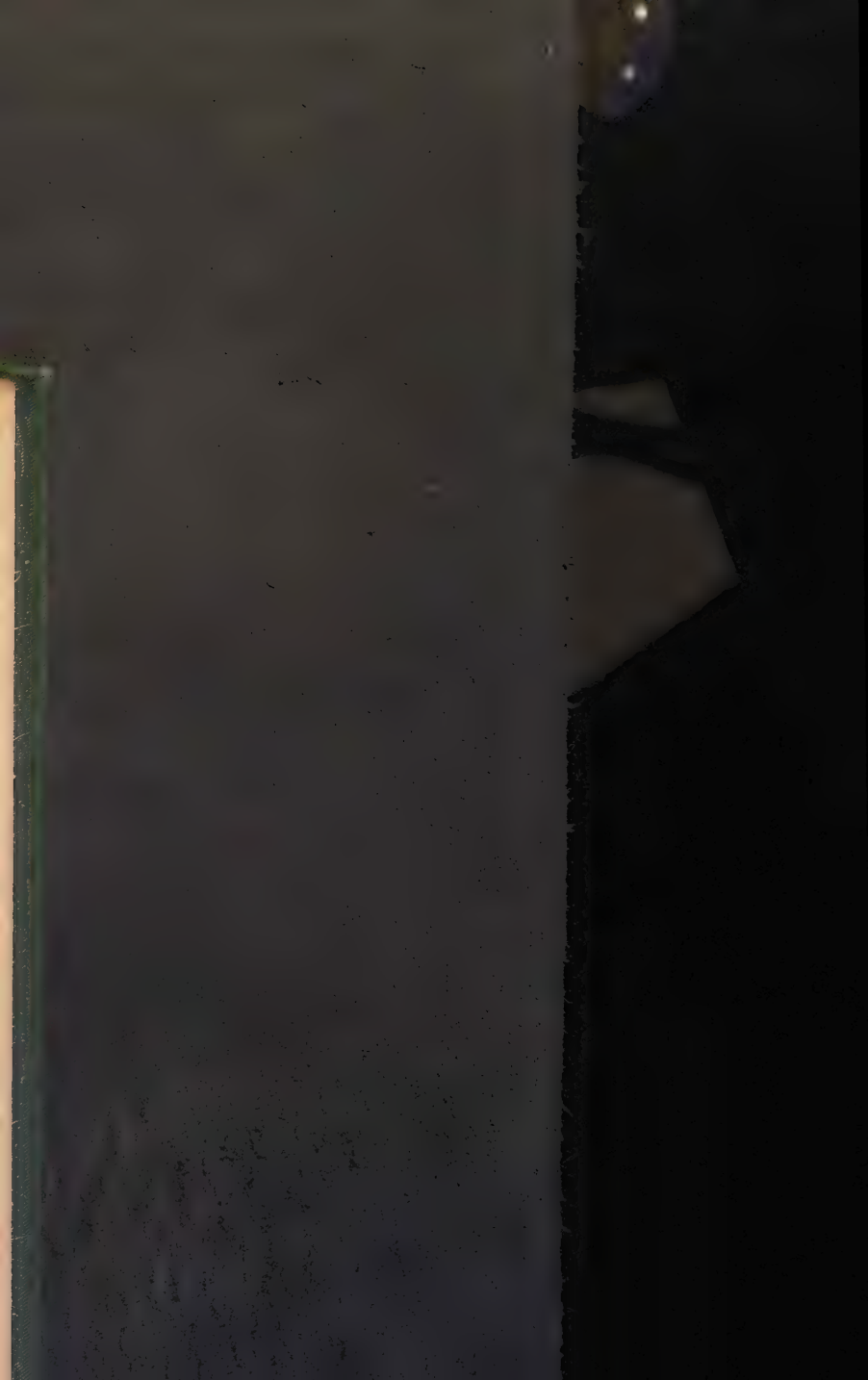
Patients with anemia in which the color index is low probably do not have pernicious anemia. Occasionally, patients with pernicious anemia in which the anemia is very mild have a color index of about one, or even a little less than one, but it is never very low. If the anemia is severe, less than two million red blood cells, the color index in pernicious anemia is always more than one and is usually quite high. Pernicious anemia is a questionable diagnosis if, in the presence of a severe anemia, the qualitative changes in the blood are not marked. The qualitative changes in the blood in pernicious anemia may not be very pronounced in the presence of a high red blood cell count but when the red blood cell count is low they usually are quite severe. In the absence of a pyogenic infection, a leucocytosis is very uncommon in pernicious anemia and if the anemia is severe, a leucopenia is always encountered. Accordingly, if a patient with severe anemia has a normal white blood cell and differential count in the absence of any cause for an increase in the polymorphonuclear neutrophiles, pernicious anemia is probably not present. Furthermore, if analysis of the gastric contents reveals a normal formula, indeed if there is any free hydrochloric acid found, pernicious anemia is a doubtful diagnosis. The author has never encountered a case of pernicious anemia which had free hydrochloric acid in the gastric contents.

The cachexia of old age may simulate pernicious anemia. Here the complexion is often sallow, one

frequently encounters an achylia, and there may be anemia. The sallowness of the elderly is not, however, the same as that seen in pernicious anemia, although it may resemble it closely. In the former it is usually merely an absence of color, or a grayish tint, differing from the peculiar yellow color of the latter. Furthermore, a discoloration of the skin in the elderly which may lead one to suspect pernicious anemia is usually only seen in them when there is emaciation and the resultant wrinkles. In pernicious anemia emaciation is most uncommon and the complexion is usually smooth. The achylia gastrica should not confuse as it is a common finding in patients in advanced age. The anemia in these patients is dependent on a general lowering of the hematopoietic, together with other functional activities and is usually readily differentiated from that of pernicious anemia. Poikilocytosis, anisocytosis, and polychromasia may be present, but are usually of minimal grade even when the anemia is severe. In pernicious anemia these qualitative changes are pronounced whether the grade of anemia be mild or severe. In the aged one may have 2,500,000 red blood cells and qualitative changes less than those encountered in a patient with pernicious anemia who has 4,000,000 red blood cells. In the anemia of the elderly there is often a moderate leucopenia as in pernicious anemia. In them, however, the leucopenia is not proportionally as severe in relation to the number of red blood cells; and, contrary to the findings in pernicious anemia, there is always a good percentage of polymorphonuclear cells even though the total white blood cell count

be lower than 5,000. In the same manner platelets are always present in good numbers in the anemia of the aged. If no blood destruction is going on there will be no increase in the urobilin of the duodenal contents and none demonstrable in the urine. Advanced age in itself is a point against pernicious anemia because this disease is one primarily of middle age.

Sometimes carcinomatosis is very difficult to differentiate from pernicious anemia until the tumor has been demonstrated. This is especially true of carcinoma of the stomach. The color of the skin shown by these patients very often simulates that encountered in pernicious anemia so closely that it cannot be distinguished from it. These patients frequently have gastro-intestinal disturbance and an achylia gastrica, and if this is of long duration, a clean tongue and papillary atrophy. The history may be confusing. At times urobilin can be demonstrated in the urine. The anemia associated with carcinomatosis may be very much like that in pernicious anemia. The qualitative changes in the blood usually are not, but sometimes are, parallel in degree with the anemia, and a leucopenia with some diminution in polymorphonuclear percentage may be encountered. Nucleated red blood cells are very often seen in anemia of malignancy. It is most unusual, however, for all these features to be present in one case, and especially in a case in which one is unable to demonstrate a tumor or some sign or symptoms pointing to this diagnosis. The possibility of carcinomatosis being incorrectly diagnosed pernicious anemia, and the reverse, is one which certainly



however, other characteristic features of pernicious anemia are lacking. Uncomplicated pernicious anemia never causes a high fever, the prostration is not extreme, and of course the special features of each acute infection are entirely lacking. When all the features of the case are presented no difficulty in diagnosis exists. But it is well to remember in examining blood films without any information in regard to the patient, that even acute infections can show a blood picture resembling somewhat, at least, that of pernicious anemia.

Two chronic infections with anemia which may possibly confuse with pernicious anemia should be mentioned. They are malaria and syphilis. Acute malaria with its typical paroxysms of chills and fever and easily found malarial parasites in the blood never causes any difficulty. In patients suffering with chronic malaria there is often a mild fever, enlargement of the spleen, an anemia with a moderately elevated color index, and urobilin in the urine with markedly increased amounts of urobilin in the duodenal contents. The spleens of these patients are usually quite markedly enlarged while enlargement of the spleen in pernicious anemia, although common, is rarely pronounced. The enlargement of the spleen in chronic malaria is possibly surpassed only by that seen in the leukemias, especially myeloid, in Gaucher's Disease, and in tuberculosis of the spleen. The anemia associated with chronic malaria, often very severe, may show a color-index quite high; and regularly, also a polymorphonuclear leucopenia is present. Qualitative changes in the red blood cells, however, are absent or very slight, even

when the anemia is severe, thus permitting a differentiation from pernicious anemia to be made readily. The stomach contents of malaria patients one may expect to find containing free hydrochloric acid; and unless by chance the malaria is associated with an achylia gastrica, the tongue will be furred heavily instead of clean, and there will be no papillary atrophy. Upon the demonstration of the malarial parasite in the blood, a diagnosis of pernicious anemia is not further to be considered until the condition is found to persist after very prolonged and vigorous antimalarial therapy.

In tertiary syphilis a blood picture is sometimes encountered which cannot be differentiated from that of pernicious anemia even by the most experienced. These patients often show a slight enlargement of the spleen, and possibly a mild irregular fever. They may also show evidence of scleroses of the spinal cord. They do not, as a rule, have an achylia gastrica or papillary atrophy, but it can occur. The author has seen one such case, the patient a male negro, in which the diagnosis of pernicious anemia was so completely justified that it was held in spite of a positive Wassermann test until the condition, with the exception of the cord symptoms, cleared up completely under antiluetic treatment. Pernicious anemia may at best be presented, therefore, only as a tentative diagnosis in the presence of a positive Wassermann test; and when expressing an opinion from a blood film alone, this reservation should be made, however typical the blood picture may be.

Infestation with parasitic worms, especially of the intestinal tract, commonly results in chronic anemia. Hookworm infestations are especially notorious in this regard and *Dibothriocephalus latus* is reported to give an anemia resembling that of pernicious anemia very closely indeed. An anemia of only moderate severity caused by hookworm differs from that in pernicious anemia in that the qualitative changes in the red blood cells are not pronounced, and there is no diminution in platelets or in polymorphonuclear cells. It may be associated with a mild eosinophilia, but as this also occurs occasionally in pernicious anemia it is not a helpful diagnostic point. When the hookworm infestation has been of long duration and the anemia is very severe so that the blood is more or less aplastic, a polymorphonuclear leucopenia may be present. These patients, although pale, do not have the lemon colored tint of pernicious anemia, and in them more or less emaciation is often encountered. The papillary atrophy of the tongue, the achylia gastrica, the fever and nervous symptoms of pernicious anemia are not characteristically present. The spleen is frequently enlarged slightly as in pernicious anemia. Despite all this, however, the diagnosis should be strongly suspected even before the worms and their ova have been found in the stools; and after this, of course, the possibility of pernicious anemia can be ruled out.

Infestation with *Dibothriocephalus latus* may exist for many years with only a mild anemia which could in no way be confused with that of pernicious anemia. Eventually most patients, probably because of absorp-

tion of digestive products of dead segments of the worm, show a more severe anemia said to be quite characteristic of pernicious anemia. If the patient comes from a locality of the world (Finland, Hungary, Russia) in which this malady is common, diligent search of the stools for segments of the worm and its ova should be made, and anthelmintic treatment carried out thoroughly before a diagnosis of pernicious anemia is suggested. It is the author's opinion that *Dibothriocephalus latus* anemia is popularly considered as difficult to differentiate from the clinical syndrome of pernicious anemia only because the studies made on this disease were principally in earlier times before the complete clinical picture of pernicious anemia had been drawn and when a chronic anemia with a high color-index and qualitative changes in the red blood cells was considered sufficient for a diagnosis. Probably now, anyone who had had much experience with true pernicious anemia would have little difficulty in most instances in differentiating the two conditions, even before the presence of the worm had been demonstrated. This opinion, however, is based on too little experience with *Dibothriocephalus latus* anemia to be given much weight.

Next to the exceptional case of tertiary syphilis, tropical sprue may occasionally resemble pernicious anemia more closely than any other disease. There is an achylia gastrica associated with troublesome diarhea and the tongue is clean and often shows papillary atrophy. The spleen very often is slightly enlarged just as in pernicious anemia and there may be a mild

fever. There is a feeling of lassitude and progressive weakness which may be associated, as in one case seen by the author, with neuritic symptoms of the lower extremities. The anemia may be severe, may and commonly does have a color-index greater than one, is often associated with fairly pronounced anisocytosis, poikilocytosis, and polychromasia; and there is a polymorphonuclear leucopenia. Most confusing of all perhaps is the history of progressive weakness with intermittent periods of diarrhea, gastric distress, and anemia over several years. In sprue the tongue is frequently ulcerated and in worse condition than in pernicious anemia even when the atrophy is extreme and the furrowing most marked. The character of the stool differs in sprue from that in pernicious anemia. In sprue they are putty colored, bulky, very frothy and of acid reaction; in pernicious anemia they are usually not unduly bulky, are of normal color and are not frothy. The characteristic lemon-tinted skin of pernicious anemia is not described for patients with sprue, and in contradistinction to those with pernicious anemia, they often show emaciation or give a history of extreme loss of weight. The qualitative changes in the red blood cells, although more marked than in most secondary anemias, are not often as severe as those in pernicious anemia with the same severe grade of anemia. The successful cultivation of Monilia albicans (Bahr) or Monilia psilosis (Ashford) from the tongue and stools helps in the diagnosis of sprue. This point must not be given too much weight because a yeast closely resembling that observed characteristically from pa-

tients with sprue may be cultivated rather frequently from other sources and the differentiation of the organisms is difficult even in a well equipped laboratory. Occasionally it is necessary to follow these patients for some time before a positive diagnosis may be made. As the disease progresses the gastro-intestinal symptoms predominate in sprue, and the anemia and nervous symptoms in pernicious anemia.

In certain toxic disturbances of pregnancy an anemia sometimes occurs which may resemble closely that seen in pernicious anemia. It is rare and the condition simulates the complete clinical picture of pernicious anemia in no respect other than the anemia. This anemia is mentioned only in passing to emphasize the point that pernicious anemia should not be diagnosed during the course of pregnancy; and to list another possible source of error if a diagnosis of pernicious anemia is attempted upon examination of a blood film alone. Occasionally an anemia of this type beginning in pregnancy does not clear up after the uterus has been emptied. When this occurs the disease rapidly shapes up as a clinical case of pernicious anemia and usually runs a typical course.

Very rarely aplastic conditions of the blood such as that associated with leukemia and with salvarsan poisoning may resemble somewhat the blood picture in pernicious anemia in an aregenerative stage when the red blood cell count is very low and the blood is aplastic. Usually, however, the aplastic blood pictures in conditions other than pernicious anemia are readily differentiated from it. In these the color index may be one

or a little above, but is usually much less than one. Poikilocytosis is very slight, although anisocytosis may be fairly pronounced. In pernicious anemia in this advanced stage poikilocytosis is very severe and the color index is very high. Very rarely these points of differentiation do not hold. The author has seen one patient in the late stages of Hodgkins disease, who had had extensive treatment with radium and x-ray over the previous five years, whose blood picture resembled exactly that seen in an aregenerative stage of pernicious anemia. The occasional resemblance between this group of conditions and pernicious anemia goes no further than the blood picture, however, and they are, therefore, readily differentiated when the entire clinical picture is considered.

Hemolytic icterus, both the acquired and the familial types, are diseases which when first seen are very readily confused with pernicious anemia. The author has never known a case of either type of hemolytic icterus in which a diagnosis of pernicious anemia was not suggested and considered carefully. The history is often confusing, for the story of several years of intermittent illness associated with anemia may well mislead one. These patients frequently have a slight fever, the spleen is regularly and the liver is commonly enlarged, urobilin in the urine is as frequent as in pernicious anemia, and there is an anemia of severe grade. A few points which may come out in the history are helpful. In the familial type, other members of the family having the same symptoms may be discovered and the history of jaundice from childhood which is so often obtained is

not to be expected in pernicious anemia. In the acquired type, a history of sudden onset does not suggest pernicious anemia but this point must not be given too much weight for in pernicious anemia the patient may date the onset of the disease from some acute illness. This illness, according to the patient's story, as in several cases studied by the author, may be associated with some jaundice, thus further confusing with hemolytic icterus. Associated with the anemia in hemolytic icterus anisocytosis, poikilocytosis, polychromasia and nucleated red blood cells are often as pronounced as in pernicious anemia, and there is usually also a leukopenia and diminished number of red blood cells. The color index, although it may occasionally be as much as one or a little greater, is usually less than one. In the acquired type which is the more difficult to differentiate from pernicious anemia the color index may be very low, something that is never seen in pernicious anemia. The resistance of the red blood cells to hypotonic salt solutions is lower than normal in hemolytic icterus, especially so in the acquired form, whereas in pernicious anemia it is normal or greater than normal in almost every instance. In the acquired type the autoagglutination test of Widal, Abrami, and Brûle is positive in most patients and always negative in pernicious anemia. In both forms of hemolytic icterus it is the rule to have a markedly increased number of reticulated red blood cells with the vital stain, whereas in pernicious anemia there is not any or only a slight increase in the number of these cells under ordinary conditions. Sometimes in pernicious anemia

that is in an active stage of regeneration the reticulated cells are found in rather large numbers and at these times this point is of no value in the differential diagnosis. The enlargement of the spleen in hemolytic icterus is usually much greater than that commonly seen in pernicious anemia. The jaundice when mild may resemble very closely the color of the skin in pernicious anemia. In the periods of deeper jaundice shown at one time or another by almost all cases of hemolytic icterus, it is readily differentiated from the characteristic discoloration of the skin of pernicious anemia, in which, in the absence of complications, true jaundice is never encountered. In hemolytic icterus one does not expect to find an achylia gastrica or the very clean, pink tongue and papillary atrophy which are so characteristic of pernicious anemia.

The differential diagnosis between pernicious anemia and the clinical syndrome "subacute combined sclerosis of the spinal cord" as described most clearly by Dana and by Risien-Russell, Batten and Collier is always very difficult. Attention was first called to this disease by Leichtenstern who described a series of cases as "progressive pernicious anemia in tabetic patients;" and by Lichtheim as cord changes associated with anemia. The anatomical changes in the cord in these cases may be exactly the same as those found in pernicious anemia. In any instance in which the changes are not the same, they can best be interpreted as further progress of the same process, as more severe and more rapid injury of the same nature (see page 74). These cases always have some anemia, and usually

show an anemia of severe grade. It is characteristically associated with a polymorphonuclear leucopenia, diminution of platelets, and rather marked qualitative changes of the red blood cells. The blood picture whether the anemia is mild or severe may, and indeed usually does, resemble closely that in pernicious anemia. As the disease progresses a sallow discoloration of the skin appears, indistinguishable from that seen in pernicious anemia. A diarrhea is frequent and associated with an achylia gastrica. Thus with the characteristic anemia, achylia gastrica and diarrhea, discoloration of the skin, and symptoms of involvement of the posterior and lateral tracts of the spinal cord, these cases cannot at once be distinguished from pernicious anemia in which involvement of the nervous system is severe. The disease has been divided into three stages by Russell, Batten, and Collier.

1. A stage of slight spastic paraplegia with slight ataxy and marked subjective sensations in the lower limbs
2. A stage of severe spastic paraplegia with marked anesthesia of legs and trunk
3. A stage of complete flaccid paraplegia, absent knee-jerks, absolute anesthesia, rapid wasting and loss of faradic excitability in the muscles of the paraplegic region, increase of superficial reflex excitability, absolute incontinence of both sphincters, and edema of the lower extremities and trunk

The nervous manifestations of typical pernicious anemia rarely go beyond those of the first stage above; and practically never beyond the second stage even when the involvement of the nervous system is severe.

The symptoms in these first two stages may be entirely typical of pernicious anemia. In the third stage of this disease there is marked wasting and emaciation, these points being very helpful in differentiating it from typical pernicious anemia which rarely shows muscular wasting and emaciation. The cases with subacute combined sclerosis of the spinal cord may have remissions, but they are not common as in pernicious anemia; and because these remissions consist merely of cessation of progress of the lesion and never any recovery from it, they do not, as in pernicious anemia, manifest themselves strikingly. In this condition the progress especially of the nervous lesions, is very rapid. Sometimes the symptoms from the injury to the spinal cord become far advanced before the anemia forces itself to the attention, and there may be very little anemia until the third stage is reached. Accordingly, if a patient when seen for the first time shows marked symptoms of involvement of the posterior and lateral columns of the cord and a very slight anemia not entirely characteristic, the possibility must be considered that the patient has, not typical pernicious anemia, but is in the first or second stage of "subacute combined sclerosis of the spinal cord" of Dana and Russell. If seen in the third stage for the first time, the muscular wasting, emaciation, loss of sphincter control, etc., together with a history of rapid progress and no pronounced remissions, usually permit a clear-cut diagnosis. When a patient with anemia shows first mild and then marked spasticity and subjective sensations which change, often suddenly, to a flaccid paralysis and loss

of sphincter control, this malady should be suggested to the diagnostician. If the anemia is severe and the picture entirely typical of pernicious anemia it is questionable whether any diagnosis other than pernicious anemia is justifiable, however severe the involvement of the spinal cord may be. It should be recognized, however, that the nervous symptoms are more pronounced than usual and that in these cases progress is usually more rapid. Occasionally borderline cases are found in which a differential diagnosis between these two conditions may not be made. Indeed it is very reasonable to suppose (see page 74) that pernicious anemia and "subacute combined sclerosis of the spinal cord" result from the same underlying disturbance, because pernicious anemia usually shows some involvement of the spinal cord as seen in some stages of the "combined sclerosis" cases, and these in turn always have an anemia characterized by the same features found in pernicious anemia. It is convenient to think of these two diseases as the same malady, in one the spinal cord being primarily attacked, and in the other, the sheaths of the red blood cells. Be that as it may "subacute combined sclerosis of the spinal cord" should be kept in mind in relation to pernicious anemia, and if not considered a separate disease from pernicious anemia, it should be diagnosed and recognized as an interesting and important variation of it.

The findings in these conditions should never confuse with regard to other lesions of the spinal cord. The absence of the immobility of the pupil to light stimulation; the history of increased knee-jerks before they

disappeared, Babinski's reflex, that sure sign of involvement of the pyramidal tracts, effectively rule out tabes. Syringomyelia may be suggested in later stages when the sensory disturbances may be the same; but in such a situation, the history, characteristic blood picture, and the sensory findings limiting the lesion almost entirely to the dorsal and lateral columns should make the diagnosis. Tumors of the spinal cord and myelitis differ both in history, symptoms, and in other features of the case.[1]

[1] The entire subject is discussed in full in a book published by Paul Hoeber, New York, 1922: Multiple Sclerosis (Disseminated Sclerosis). An investigation by the Association for Research in Nervous and Mental Diseases. Charles L. Dana, and collaborators.

CHAPTER VII

Treatment

The treatment of pernicious anemia is discouraging. No patient with true pernicious anemia has ever been cured. However successful any therapeutic procedure may have been at first, there comes a time when the patient does not react to any treatment, he gradually grows worse, and death ensues. Furthermore, no treatment has so far been suggested which can be shown to have prolonged life. Because the etiology is unknown, no measures designed to influence in the right direction the causal factor of the disease can be instituted. The treatment in pernicious anemia is, therefore, symptomatic, calculated to improve the condition of the patient while he is alive, to keep him more comfortable, and to prolong life if possible. All but a few patients when first seen will react to certain therapeutic measures and have periods of remission, sometimes often, sometimes only once or twice, for it is one of the fundamental characteristics of the disease to have periods of improvement. These periods of remission often occurring spontaneously with little or no treatment make it particularly difficult to estimate truly the value of any measures carried out. Many things can be done for these patients, however, that unquestionably improve their condition, even though temporarily, and keep them more comfortable; and it is the author's firm conviction that remissions, even

though occurring spontaneously, can frequently be hastened, even possibly induced, when the patient is not in the late stages when he is refractory to any treatment and death is imminent.

General, simple, upbuilding measures are by far the most important of any in the treatment of patients with pernicious anemia. Indeed, it is problematical if any other measures instituted would be of much value without this. Absolute rest in bed over considerable periods of time is the most helpful feature of this regimen. The weakness and general malaise, shortness of breath, edema, and other distressing symptoms frequently improve with rest in bed alone, and cessation of improvement or relapse not infrequently occurs as soon as activity is again resumed, in spite of continued medicinal and other therapeutic procedures. While in bed mental and spiritual rest should be enjoined as far as possible, and the patient should have plenty of fresh air and sunshine. Special measures to keep him warm should be taken when necessary. The diet should be bland and nourishing, and should not, as advised by some, be primarily vegetarian. These patients may want meat, and they should be given it, as it does them no harm when the achylia gastrica is controlled by treatment. A high protein diet may be of value. Whipple and Robscheit found that blood regeneration in dogs with an anemia induced by hemorrhage was much more rapid on a high protein diet than under any other circumstances. Mosenthal reported improvement in each case of a short series in which he induced a definite nitrogen retention by high protein

diet. The possibility of the disease being caused by some disturbance of lipoid metabolism tempts one to limit the fats. But inasmuch as no practical information on this subject is as yet available, and a nourishing diet without fat is very hard to make up, this cannot be advised.

In view of the achylia gastrica constantly found in pernicious anemia, a diet sufficiently nourishing can often not be given to these patients without causing them considerable distress and resulting in a wasting diarrhea which may be disastrous. An important feature in the treatment of pernicious anemia is, therefore, directed toward overcoming this. Dilute hydrochloric acid (Acidum hydrochloricum dilutum, N.S.P.) is usually efficacious. The treatment should be started with 10 minims in water after meals. If this does not prove to be effective more should be given until the diarrhea which may be so distressing a symptom is entirely controlled. At the same time the condition of the tongue, which is often sore and furrowed, usually improves. The papillary atrophy and pink appearance persist, but it ceases to annoy the patient and he can eat his meals with more enthusiasm. Hydrochloric acid should be given as a routine whether there are gastro-intestinal symptoms or not, and it should be continued.

The value of medicine is open to question. Iron in various forms was used in the past but has long since been discarded as useless. In the hemolytic anemias there is no iron starvation. The blood is destroyed in the body, and the iron is carefully conserved. That the

organism has plenty of iron is shown by the high content of each individual red cell in iron-containing hemoglobin; the high color-index shows that each red blood cell contains more hemoglobin than it does under normal conditions. At autopsy the tissues are found loaded with iron containing pigment. Even in secondary anemia in dogs induced by bleeding and in which the iron was lost to the organism, Whipple and Robscheit found no more rapid regeneration of the blood when iron was administered in various soluble forms than when it was withheld, the same general conclusions being arrived at by Musser after the same type of investigation.

Arsenic is widely used and is advised by many careful clinical observers. It is usually given as Fowler's solution in increasing doses, or as sodium cacodylate. If Fowler's solution is used it should be started with 3 minims in water three times a day and increased 1 minim each dose every day until 10 minims three times a day are being given. Sodium cacodylate, if this is used, should be given in 1 mgm. doses intramuscularly once every day, or every other day, for ten doses, and then discontinued for several days or a week. Salvarsan in small doses has been used but cannot be advised. The danger is too great and since other methods of administering arsenic are satisfactory, it should not be used. Arsenic probably is of value as a general tonic and as a hematopoietic stimulant, but no real benefit from its use can be proved (Minot and Lee). When it is used, one should remember that what is a hematopoietic stimulant may be in larger doses a

hematopoietic poison. In animals a very severe anemia may be induced by arsenic administration, and one of the results of salvarsan poisoning in susceptible individuals is an aplastic anemia (Moore and Keidel, Gorke, and Evans). Mosse reports a distressing pigmentation of the skin in a patient with pernicious anemia which he feels is dependent upon prolonged treatment with Fowler's solution. Furthermore, in pernicious anemia there is probably already an overstimulation of the hematopoietic function. It is not responding normally probably because it is incapable of doing so rather than because it is understimulated. One must remember, therefore, that in using arsenic in pernicious anemia he may be whipping up an already overdriven, tired horse working over rough roads, thus hastening the final collapse rather than promoting real progress.

Hammett, Mowery and Muller reported what they believe to be a very active hematopoietic stimulant in germanium dioxide. They found an increase of from one to five million in the red blood cell count of adult white rats when this drug was administered in the proper dosage. The increase was prompt in appearance, following in one week the administration of the drug, and subsided rapidly. Mowery later reported that germanium dioxide in neutral solution has little if any stimulant action on the hematopoietic activity of rats, but that a solution of sodium germanate does have this property. Bodansky could demonstrate no such activity for germanium dioxide in rabbits rendered anemic by phenylhydrazine poisoning or in dogs with

hemorrhagic anemia. This drug was administered by Muller and Iszard to a normal adult man and a similar prompt and pronounced increase in the red blood cell count was noted. Alexander gave 100 mgm. per kilogram of body weight of germanium dioxide to 3 patients with pernicious anemia. None of these patients showed any clinical improvement with the treatment even though they were not in the late refractory stages as shown by subsequent improvement under different treatment. Germanium dioxide was used by Stengel, hypodermically or by mouth, in doses varying from 0.1 to 3 mgm. per kilogram of body weight in 13 cases. At first small doses were given hypodermically. Later larger doses hypodermically were used, and finally massive doses by mouth. He reported no improvement in any of the cases. So far the results are discouraging. Should other studies prove more hopeful and some compound of germanium be found to be a hematopoietic stimulant, when so used the same considerations pointed out for the use of arsenic for the same purpose, should hold.

Holler reported finding no iodine in the thyroids of patients with pernicious anemia and for this reason gave to them small doses of iodine, 3 to 5 drops of a 5 percent solution of potassium iodide three times a day, over long periods. This medication did not cause immediate improvement so was combined with arsenic at first. The long continued iodine administration was found by Holler to result in permanent improvement. One of these cases said to have had not only pernicious anemia but pulmonary tuberculosis also was reported as cured.

Proescher reported studies by himself and by Plesch, Beckel, Gudzent, Kemperer, Hirschfield and von Noorden on the use of thorium X and radium in pernicious anemia. These substances are unquestionably hematopoietic stimuli and should be considered in the treatment of pernicious anemia as substances to be used, but to the use of which the same considerations apply as to other drugs of such action. Proescher pointed out the dangers attending larger doses of either drug and stated that soluble radium salts are very much less toxic than thorium X.

Roentgen-ray exposures to the splenic area have been tried but no appreciable improvement has followed. Minot and Lee applied this treatment without benefit to three cases of hemolytic icterus, a disorder very beneficially influenced by splenectomy.

Heuer has noted marked improvement in several cases of pernicious anemia after systematic treatment with the mercury vapor lamp. Cholesterol has been shown to be a very active absorber of these rays (Hess, Weinstock and Helman) and cholesterol, an antihemolytic agent, is diminished in pernicious anemia. Can we reason by analogy from Park's observation that these rays in the presence of a minimum of calcium and phosphorus prevent rickets by promoting maximum utilization of that present, that they similarly bring about a maximum utilization of the cholesterol present in pernicious anemia? First, the rôle of cholesterol in hemolytic anemias must be explained; but this suggestion invites further study.

Since Hunter suggested a streptococcus infection of the upper alimentary tract, all manner of foci of infec-

tion have been suggested as the etiology in pernicious anemia. This, however, seems quite unlikely in view of the high incidence of such focal infections without evidence of pernicious anemia. They rather induce simple secondary anemias. In spite of this, any focus of infection found in a patient with pernicious anemia should be eliminated, if possible, not with the expectation of removing the causal factor, but for their own sake and for any general beneficial effects which may follow. Of course when any focus of infection is so located that the shock of operation or anesthetic would be great, judgment must be used in advocating its removal. As a general rule, however, as part of the general measures for building up the patient, close attention to foci of infection should be emphasized.

Blood transfusion is a method of treatment which gave more promise and has been given wider study than any other ever considered. In pernicious anemia the method used seems to be of no importance, and inasmuch as the indirect transfusion of citrated blood is the most convenient and is most easily carried out, it may be used. It is true that citrated blood by reason of changes in it caused by the citrate, probably alterations in the red blood cells and platelets (Drinker and Brittingham) may give rise to reactions where the direct transfusion of blood does not. But these reactions are so slight that if the blood of donor and recipient are properly matched and other necessary precautions of blood transfusion are taken, and there are no other contraindications, they may be disregarded. Even the citrate method of blood transfusion is not

simple, however, and a transfusion by any method is not wholly innocuous. Blood transfusion should not, therefore, be carried out thoughtlessly; it should be decided upon only after careful consideration of all the features of the case. Furthermore, the number of blood transfusions one patient may take is limited (Bowcock, and Stansfeld) and if they are of any value, they should not then be used unnecessarily.

The exact manner in which blood transfusions operate in benefiting the patient is not understood. That the transfused cells live and probably function as oxygen carriers is evidenced by the work of Ashby and of Wearn, Warren and Ames. These latter observers found the transfused red blood cells in the circulation of the recipient as late as the one hundred and thirteenth day after transfusion in one case, the average life of the transfused cells in a number of patients, including some with pernicious anemia, being eighty-three days. Usually, however, the amount of normal blood introduced in the circulation of the patient is not sufficient to account, by the increase in oxygen carrying tissue alone, for the improvement resulting. Even after large transfusions Huck was unable to demonstrate any constant increase in the number of circulating red blood cells. This observation may not give a correct impression, however, for Ashby has shown that following transfusion there is often a change in blood volume. She found a passage of fluid from tissues to blood after the first transfusion, and the reverse after later ones.

Very often the transfusion of a small amount of

blood will result in as much improvement as a massive transfusion. It is possible that the introduction of normal blood exerts in some manner a beneficent effect on the process of hematopoiesis. If this is so it must be in some other way than simple stimulation for, as already pointed out, such additional stimulation is probably not needed in pernicious anemia. It is possible that the transfused blood introduces a little excess of antihemolysin, or an antibody to some toxin, this resulting not only in a diminution in the rate of blood destruction, but also in an increase of blood formation because of the release from inhibition of the hematopoietic tissues. The finding of Clark and Evans that the diminished antihemolytic power of the serum in pernicious anemia is increased after transfusion, supports this suggestion. The improvement in the general condition of the patient, especially in his subjective feeling of well-being, so very frequently following a blood transfusion or even the introduction of a compatible human serum, make it easy to assume that by it we have introduced some antitoxin to a circulating poison. If this antibody is cholesterol as at least seems possible, the finding of Kipp that the cholesterol of the blood is only momentarily increased after transfusion, would indicate that it is promptly used up in neutralizing some substance. An immediate rendering inert of even some poison would explain the improvement noted.

The benefit derived from a transfusion may result from some reaction in the nature of a mild protein-shock. We know that some cases of pernicious anemia

can be benefited by subcutaneous or intramuscular injections of whole blood or serum and even by injections of foreign proteins (Faber). No doubt the answer to this question will be compelled to wait for the demonstration of the etiological factor in pernicious anemia. It seems almost certain, however, that the original reason for the use of blood transfusion, the introduction of more blood in an anemic patient, no longer can be held alone in pernicious anemia.

There are very few contraindications for transfusion in pernicious anemia. One should always keep in mind that however carefully the bloods of donor and recipient have been matched, and however cautiously the blood has been given, some reaction is bound to follow. Drinker and Brittingham present studies which leave no doubt as to this, those transfusions which we formerly thought were unaccompanied by reaction, having such a transient elevation of temperature and other disturbances that our routine methods of observation missed it. If, for any reason, the additional strain of even a slight reaction is to be avoided, transfusion should not be carried out. This observation applies with great force to traumatic or hemorrhagic shock, where subcutaneous infusion of normal salt solution should be employed instead during the first few hours when the patient is in very bad condition. In pernicious anemia this rule may not be made so positive. Sometimes a transfusion will apparently save the life of a patient very ill with pernicious anemia, whereas it would have killed a patient in equally bad condition from hemorrhage or from traumatic shock.

The decision for or against a transfusion in these situations for a patient with pernicious anemia becomes very difficult and demands sound clinical judgment. Another contraindication to transfusion is the possibility of a severe reaction in a patient who, by reason of repeated transfusions, has developed antibodies for compatible bloods. Some patients may take twenty or more transfusions without difficulty while others after sixteen or eighteen may show agglutinins or hemolysins for any blood tried. Sometimes the blood of one donor will become incompatible for the patient after several transfusions. When this occurs another donor from the same group should be tried. Often several transfusions may be taken from this second donor when his blood in turn becomes incompatible. After the use of several donors, a stage is eventually reached where any blood is incompatible and further transfusions are impossible. One of the most dangerous points about this situation is that this incompatibility of the patient's blood for any other may be, indeed very often is, not demonstrable in vitro. The result is that a very sick patient may have a severe transfusion reaction resulting in irreparable damage. If, for any reason, such general incompatibility of the patient's blood is suspected the whole blood should be given intramuscularly or subcutaneously or he should be given the serum alone from Group IV (Moss classification) donor. Some of the severe reactions after many transfusions do not seem to be those of incompatible bloods. Minot and Lee suggest that they are due to a super-saturation of the tissues with blood pigments

and refer to the case studied by Sellards and Minot which was definitely shown to be sensitive to hemoglobin after several transfusions at short intervals. The author has seen one patient in which Group IV serum alone induced a very severe reaction followed in two weeks by death. Finally, a transfusion should not be given unless it is truly needed. The number of transfusions any patient may take is limited, and if they are of value, they should not, therefore, be used unnecessarily. When a remission is imminent or in progress no transfusion is called for. It is difficult to predict an oncoming remission before it gives evidence of itself in an improved blood picture. As a rule, however, if the patient says he is feeling better, if he is eating with some relish, and edema and dyspnea have disappeared, a remission is likely in progress and will show itself in an improvement in the blood picture in a few days. Recently Evans called attention to the differential white blood cell count as an additional aid in predicting an oncoming remission. He found that an increase in the absolute number of polymorphonuclear leucocytes, however low they may have been, usually preceded by several days other changes in the blood accompanying a remission. And, conversely, a decrease in the polymorphonuclear leucocytes however high they may be, frequently was found when a relapse was imminent.

Blood transfusion in pernicious anemia is indicated when the patient is severely ill and does not react to rest in bed, a hygienic regimen, hydrochloric acid, and possibly arsenic. At these times a remission may be

induced by a whole blood transfusion, or if impending may be hastened. A transfusion may also be useful during the course of a remission which appears to have been arrested. When a relapse is imminent as shown by the subjective feelings of the patient, a drop in the absolute number of polymorphonuclear leucocytes, and cessation of progress, a whole blood transfusion may in many instances, and almost surely does in some, abort it. When a relapse is in progress, a transfusion not rarely, but frequently, will arrest its downward march, and will sometimes alone, but usually aided by another, change a discouraging outlook into one more hopeful.

If one expects too much from blood transfusion, he will be disappointed. An analysis of cases by Bloomfield to determine what benefit, if any, is to be derived from this method of treatment showed that life was not prolonged by it. The duration of the remissions were no longer in cases which had had transfusions than in those which had not, and the number of relapses recovered from before the patient finally became refractory to any kind of treatment was not increased. These studies also throw light upon the value of transfusions in very sick patients, and aid one in making a decision for or against a transfusion in an effort to tide over an emergency. Of the patients with red blood cell counts under one million, 33 percent of those given transfusion, and only 20 percent of those who were not transfused, died in the hospital. The series of cases is very small but weight is given to these figures by comparison with about the same number of patients with red blood cell counts over one million. Of these, 11

percent who had been given transfusion, and 17 percent of those who had not been transfused, died in the hospital. These statistics indicate that a blood transfusion may not be the thing to do when the patient is very ill, and that as an emergency measure it must be employed only after careful consideration. That the reaction, however small, following any blood transfusion may be detrimental, in pernicious anemia, as in patients suffering from traumatic shock or severe hemorrhage, has been the impression of several clinicians treating many cases of pernicious anemia and Bloomfield's statistics lend support to this opinion. On the other hand, the cases analyzed by Bloomfield show that transfusion brought about an earlier onset of remission and greater improvement in the blood picture and general condition of the patient. Among these patients more prompt and greater improvement resulted from large transfusions than from the smaller ones. Minot and Lee analyzed the results of transfusion in 46 patients with pernicious anemia. Inside of several weeks there was definite improvement of the blood picture beyond a simple filling up of transfused blood in 50 percent, and slight improvement in 13 percent. These authors are very careful in drawing conclusions as to the benefit to be derived and call attention to the fact that the patients in whom the best results are obtained are those who are most likely to have remissions anyway and who react best to any treatment. Probably the most beneficial effect of transfusion is the alleviation of distressing symptoms. Shortly after a transfusion, a patient who has been very miserable

will commence to feel better. He becomes more cheerful, his weakness, dizziness, palpitations and sometimes nausea cease to annoy and his dyspnea becomes diminished or disappears. Frequently also the fever falls and gastro-intestinal symptoms tend to be less distressing. Of course all these improvements are coincident with an improvement in the blood picture and often result from rest in bed and other up-building measures outlined above; but the improvement in these features is often so prompt after a transfusion that they could not be due to general improvement in the condition of the patient. Occasionally even patients who are so far advanced that they fail to react to a transfusion will, in the absence of a remission, have several days of subjective improvement and comfort following it. Improvement in the nervous symptoms is not found after transfusion, any more than after other methods of treatment. The symptoms come from a sclerosis of the spinal cord which once accomplished remains as it is or progresses but never improves.

There is much difference of opinion as to the amount of blood to be given in one transfusion. Some observers maintain that large transfusions of 500 cc. or more accomplish more than small ones, while others maintain that small amounts of blood, 100 cc. or less, give just as much benefit. Certainly the smaller transfusions may be given with less reaction than larger ones, and as such are desirable. But it is the opinion of many, and the statistics of Bloomfield bear them out, that the larger transfusions cause more improvement

in the patient. Minot and Lee question the wisdom of large transfusions in every case and call attention to the period of hematopoietic inhibition often following them. Colwell reported a series of cases in which he had used very small transfusions repeated at short intervals. His patients show beyond question that blood tranfusion given in this manner is effective. In this connection the question arises whether, since the number of transfusions one patient may take is limited, the greater good in the long run may not be derived from one large transfusion rather than from several small ones. We do not know as yet whether one patient can take more small than large transfusions, and this must be investigated before the final answer to this question may be given. It would seem that both large and small transfusions should be used as indicated, that the decision should depend upon the special features of the case. It is the author's practice to use small transfusions when a transfusion is unquestionably indicated but the patient is so ill that any but the very mildest reaction is to be avoided. When the patient has been tided over the critical period so that he can stand without disaster a moderate reaction, larger transfusions are given. Under these circumstances small, repeated transfusions result in no more benefit to the patient, and may develop incompatibility for all blood more rapidly. Of course, occasionally as good results are obtained from one small transfusion as could have been expected from a large one; and when this occurs the small one was fortunately chosen. It is impossible to predict when this will occur.

Ottenberg and Libman, and Archibold give evidence to show that more benefit is derived from transfusions from some donors than from others. This certainly seems reasonable, but definite conclusions to this effect are difficult to prove; and there is no way of determining which of several donors would be most efficacious.

Minot and Lee report no special benefit from transfusions from a patient with polycythemia vera.

What then should be our attitude toward transfusions in pernicious anemia? It probably does not contribute enough additional oxygen carrying tissue to make it worth while. It does, no doubt, result in hematopoietic stimulation, but this is not needed. It possibly does afford additional antibodies for some circulating poison. It never cures pernicious anemia, and cannot be shown to prolong life. Examination of statistics does not show that the duration of the remission is prolonged. There are those who say that it does not increase the number of remissions. Some careful, observant clinicians have expressed the opinion that a patient with pernicious anemia has only a limited number of remissions coming to him, and that with the help of blood transfusions he runs through his allotment more rapidly. On the other hand small transfusions, when they can be born at all, do undoubtedly help some patients through critical periods. Furthermore, blood transfusions almost surely do sometimes induce, and more frequently hasten the onset of, remissions. They also probably abort an oncoming remission in some instances, and check many which are in progress. They surely do, in most instances,

improve the subjective feelings of the patient and give him very prompt relief, for a shorter or longer period, from some of his most distressing symptoms. Blood transfusions are then of great value in pernicious anemia as a symptomatic or palliative treatment. Sufficient information on this subject has not been collected to permit final judgment on whether they should be used as a routine treatment. They possibly do no harm, although even this is not proved. Probably the correct attitude is to use blood transfusion in pernicious anemia only after careful consideration of all the features of the case, primarily as a palliative measure and with a full knowledge of what may be expected from it, even though we do not know the mechanism by which this is accomplished.

The intravenous injection of hemoglobin has been suggested and tried (Bernheim) and encouraging results reported. This is easy to understand in the secondary anemias resulting from blood loss, where there is not sufficient iron containing pigment in the body. In pernicious anemia, however, there is enough iron containing pigment in the body if it could be properly used. For this reason it is difficult to understand how intravenous injections of hemoglobin could influence favorably the course of pernicious anemia unless it neutralizes some poison, stimulates hematopoiesis, or causes a beneficial protein shock. If it is beneficial for any of these reasons, the same could be accomplished more easily by the use of a compatible serum, and the danger of a reaction to the blood pigment as mentioned above would be avoided.

Splenectomy in pernicious anemia has been tried. The finding of Eppinger and of King that the degree of unsaturation of the fatty acids is diminished and the amount of cholesterol is increased after splenectomy, give reason for its trial. Splenectomy is a form of treatment not to be undertaken lightly, however, for it is a surgical procedure attended with rather large risks even in the hands of the most expert. Furthermore, an appreciable amount of blood is lost to the patient, in the spleen removed if no other way, and if the spleen is much enlarged this blood loss may be important. After splenectomy Minot, and Pepper and Austin, report an increased nitrogen loss changed temporarily into a nitrogen retention and a diminution in the amount of urobilin and urobilogen to be found in the urine and stools. Pepper and Austin further record a diminution in the amount of uric acid lost. Denis shows that the lecithin and cholesterol of the blood are increased after splenectomy in pernicious anemia, thus confirming clinically the experimental work of Eppinger and of King. It would seem, therefore, that splenectomy in pernicious anemia results in an increase in the antihemolytic lipoids of the blood and in evidences of decreased blood destruction. Clinical reports of the results obtained are, however, not encouraging. The results of the analysis by Bloomfield of 8 cases in which splenectomy had been performed may best be presented in his own words. "These cases furnish no proof that life was prolonged, that the remissions were longer and more marked, that transfusions were better 'held' or that there was any special relief of symptoms follow-

ing splenectomy." The same general conclusions are reached from a study of the cases reported by Krumbhaar. Vogel while noting that the benefit of transfusion was greater in the splenectomized cases, is not more encouraging as to the general results to be obtained. In 1917 Giffen studied the effects of splenectomy in thirty-one patients. At this time he reported that splenectomy was followed by a markedly favorable immediate reaction, and the majority of the patients showed a definite temporary improvement in their general condition and in their blood picture. There was also at least a temporary reduction of the hemolytic factor evidenced by the fall in the values for bile pigments in the duodenal contents. In a subsequent report dealing with 50 patients upon whom splenectomy had been performed more than three years before Giffin and Szlapka throw still more light on the subject. They report an operative mortality of 6 percent. Of those recovering from operation the evidence permits them to conclude that life was prolonged in at least 20 percent of the cases. Minot and Lee from a study of 19 cases state that "it seems rather clear that in many instances there cannot have been more than a slight prolongation of life." They did not find that real improvement followed splenectomy more consistently than any other treatment. There was greater evidence in the peripheral blood of hematopoietic activity and greater improvement in the subjective symptoms of the patient. These authors felt that the splenectomized patients responded better to transfusion, but that when relapse occurred, as they

inevitably did, they were about the same as in the patients who had not had their spleens removed. Both relapses and remissions probably progressed more rapidly. Minot and Lee suggest that cases for splenectomy should be selected. Those with the most active, though short relapses and remissions, and those that respond to transfusion, the more actively hemolytic cases, appeared to derive the most benefit from splenectomy. But these cases, the same as pointed out by Minot and Lee for transfusions, do better under any form of treatment. Our own experience and that of many others with splenectomy in pernicious anemia is no more encouraging than in the reports cited. In view, then, of the danger of the procedure and the slight improvement to be expected from it, splenectomy cannot be advised.

Faber reports from his clinic in Copenhagen very favorable results in some cases of pernicious anemia from the feeding of "kefir." Kefir is a milk in which alcoholic fermentation has been carried out, several similar products under different names being prepared in Europe and America. Faber gave his patients 0.5 liter of kefir each day and not only found improvement in some ordinary cases, but in one also which had been proved refractory to other forms of treatment. As an explanation of this improvement, Faber postulates an intestinal intoxication and suggests that pernicious anemia is a sensitization to some protein, is an anaphylactic state. This led him to try intramuscular injection of kefir and of milk, and finally of peptone. He gave intramuscularly 6 cc. of milk and reported an

improvement in the subjective symptoms within several days of the first injection. The improvement in the objective symptoms followed some time later. The same results were obtained by protein shock, however brought about. The improvement following these procedures as reported by Faber was much like that seen following blood transfusion. In these cases, also the time came when the patient was refractory to the treatment and became progressively worse till death ensued. Faber believed that remissions following this type of treatment were longer than those seen when it was not employed. Certainly such treatment is innocent enough and may well be tried. No further data are available, but it may be found to be of value.

Because of the well-known antihemolytic properties of cholesterol, cholesterol feeding has been suggested (Reicher and Pribram) and in view of the diminished cholesterol in the whole blood this certainly sounds rational. Cholesterol therapy of one kind or another is a thought which beckons invitingly. Very little data is available on the results of this method of treatment but it is not encouraging. We know too little about the digestion and absorption of cholesterol to explain what happens when cholesterol dissolved in oil is fed. Probably most of it is lost in the stool. Until the solvents for cholesterol are found, until we know more about the normal digestion, absorption and utilization of lipoids, and until some definite, practical disturbance of lipoid metabolism is demonstrated, no rational recommendation for the use of cholesterol in any manner may be made. There are definite con-

traindications to using it other than by mouth, for injected intravenously or intramuscularly it acts as a foreign body. It is taken up by the foreign-body giant cells, the so-called vitally staining histogenous macrophages or reticulo-endothelial cells. If administered over long periods in large amounts to animals these cells loaded with the non-metabolyzable lipoid become very numerous, so-called Anitchkow cells, and may result in a histological picture such as is occasionally encountered in certain lipemias of childhood. Two such cases have been reported by Knox, Wahl and Schmeisser under the name of Gaucher's Disease. Furthermore, Klotz has shown that cholesterol dissolved in oil when injected into rabbits, is deposited in the media of the arteries resulting in degenerative changes, thus inducing medial arteriosclerosis. Cholesterol therapy, however suggestive and inviting may not, therefore, in any form, be advised in pernicious anemia at present.

All that has gone before applies to pernicious anemia as a true clinical syndrome. The first thing in the treatment of any disease suspected of being pernicious anemia is to make the diagnosis sure. If the disease under investigation proves to be, not true pernicious anemia but some condition with features, especially the blood picture, closely resembling it, a cause should be demonstrable. When this cause is found, be it a source of chronic bleeding, a source of chronic debility, a parasite, syphilis or what not, treatment should be vigorously prosecuted and marked improvement, if not complete cure, may be expected.

To sum up, the treatment of pernicious anemia is discouraging. Because the etiology is unknown no rational procedure calculated to correct the basic disorder can be instituted. No patient can be cured of pernicious anemia, and it is extremely questionable whether life may be prolonged. Therapeutic measures are, therefore, primarily palliative and are largely symptomatic. The patient should be put to bed and kept warm, should be given a maximum of fresh air and sunshine. The diet should be bland and nourishing, and nothing that is not definitely undigestible should be eliminated from it. Hydrochloric acid should be given by the mouth as soon as the diagnosis is made, and should be kept up. Arsenic in the form of Fowler's solution or sodium cacodylate may be used. To hasten or induce a remission, a whole blood transfusion may be given. If the patient is severely ill the blood should be given in small quantities at first, if at all. Later, when a blood transfusion is indicated, larger ones may be given. If, in the later stages the patient develops antibodies for any blood, the blood may be given subcutaneously, or the serum from a compatible blood group given intravenously, intramuscularly, or subcutaneously. Instead of this, intramuscular injections of peptone, or milk, or some other foreign protein may be tried. If the whole blood is given subcutaneously the patient should be forewarned of the blue discoloration resulting in the area of the injection. Systematic treatment under the mercury vapor lamp is certainly harmless and should be tried.

CHAPTER VIII

Prognosis

The prognosis in pernicious anemia is discouraging. The patients never get well and the expectation of life is not for a long period. The probable duration of life is hard to predict because the tendency of pernicious anemia to have remissions, which even in the later stages may be so complete as to approach normality leaves nothing except the history to guide the physician as to what stage of the malady the patient is in when first seen. And the history may be misleading. The disease is insidious in its onset and no doubt does not become apparent until it has been existent for some time. Furthermore patients with manifest pernicious anemia seem to compensate for the anemia in some manner so that they may show very little reaction to an anemia of severe grade. For this reason they do not report early to the physician. It is likely, therefore, that almost all cases of pernicious anemia seen by physicians have been progressing for some time before the patients feel ill enough to consult them, and any but the most casual and rough estimation of the total duration of the disease is impossible.

Many of the patients with pernicious anemia are dead within three years of the time they first consult a physician, and probably the majority of them do not live longer than four years. Practically no patients are alive five years after the diagnosis has been made, although a few isolated cases reported by Haden and

others lived for periods longer than this. Life longer than five years is so absolutely the exception, however, that one may not indulge wisely in any such favorable prognosis. The expectation of life in pernicious anemia is, therefore, not cheerful.

In regard to the immediate future one may, after several days of observation, very frequently render an encouraging prognosis. Unless the patient gives a long history of relapses and remissions, one can with a fair degree of assurance, however ill the patient may be at the time, promise early and marked improvement. The author has never seen a patient who could from the history be recognized as an early case, who did not show very extensive improvement under treatment. Indeed, if such does not occur, either the correctness of the history or the diagnosis should be seriously questioned. Sometimes improvement is slow in making its appearance, but more often it is fairly prompt. Those patients in whom there is less hemolytic activity in progress as evidenced by a small amount of urobilin in the urine, stool and duodenal contents may be expected to improve more promptly than those having much urobilin.

With the administration of hydrochloric acid by mouth, distressing gastro-intestinal symptoms usually disappear with gratifying promptness, so that within a week the diarrhea has been checked, the soreness of the tongue does not annoy so much, and the feeling of repulsion for food is markedly diminished. Within two weeks the patient should eat without distress. After a week or two in bed such patients usually suffer

very little more from weakness, from headache, or from palpitations. Sometimes edema when present, will not clear up so promptly.

All the changes mentioned may take place with little or no improvement in the blood picture. One cannot predict with any degree of assurance when the anemia will begin to improve or the rapidity of its progress. Sometimes this commences early and progresses rapidly, this usually occurring in patients who do not complain of much general discomfort or malaise when first seen. If the patients are quite ill and the anemia is very severe, the blood counts showing less than 1,500,000 red blood cells, and especially if the blood platelets are very low or almost absent, and the total number of polymorphonuclear cells are markedly diminished, improvement of the anemia may be very slow. Indeed, in spite of improvement in other features of the case, the severity of the anemia may persist for a long time unless a blood transfusion is given. Even then improvement in the blood picture, while frequently resulting, does not always promptly follow, and one or more additional transfusions may be necessary before the upward progress becomes manifest. When about to give a transfusion one may promise with great assurance, however, that the annoying subjective symptoms of the patient will be somewhat ameliorated.

One has no sure way of predicting the extent of a remission, or when it is accomplished, its duration. If the blood shows some platelets and a fair number of polymorphonuclear cells, or if these elements are prompt in making their appearance in larger numbers,

an extensive improvement in the blood picture is more likely to occur than if the platelets remain absent and the polymorphonuclear neutrophiles are scanty and do not increase. When, after a transfusion, the number of reticulated cells seen after staining with brilliant cresyl blue are numerous, more extensive regeneration of the red blood count is likely to follow than if they are few in number. If a number of nucleated red blood cells, *normoblastic in type* appear it is also a good sign, but the absence of these cells is not of bad import. Many very extensive remissions occur without the appearance in the peripheral circulation of more than an occasional nucleated red blood cell. The presence of nucleated red blood cells is encouraging only if they are principally normoblastic in type. If they are younger, are predominately megaloblasts or gigantoblasts they are, on the contrary, a bad sign. They indicate a bone-marrow nearing exhaustion and a pronounced remission is not to be expected. One of the most helpful aids in predicting the extent of a remission is the general subjective feeling of well-being or the reverse presented by the patient. Some patients when feeling very well do not have extensive or rapidly progressing remissions; but few remissions ever start, or if started continue, if the patient is feeling badly. When the activity of the underlying disturbance causing the disease is diminished, it becomes apparent in an improvement in the general subjective symptoms of the patient sometime before the blood has had opportunity to show improvement.

As with the time of inception, rapidity of progres-

sion, and extent, so with the duration of a remission, reliable predictions in regard to it are difficult. Remissions in the earlier stage of the disease are likely to be longer than in the later stages. Usually also, remissions which begin promptly after treatment has been instituted, and are very pronounced, are of greater duration than those only appearing after prolonged treatment, after transfusion, etc., and which only show after some time a moderate regeneration of red blood cells. If a remission is very pronounced so that the patient is discharged from the hospital with more than 4,000,000 red blood cells, one may reasonably expect it to be of long duration. One patient who, under the author's care was discharged after having been given but one transfusion, with 4,000,000 red blood cells and a total white blood count of 7,500 with 76 percent polymorphonuclear cells, went to work and was apparently well for twenty-one months. Another patient who had been given no blood transfusions and was discharged with a red blood cell count of 4,800,000 and a normal total white cell and differential count remained well for seventeen months. Occasionally longer remissions than this are encountered, but they are the remarkable exceptions. Sometimes, however, patients with high red blood cell counts have relapses early. One such patient seen by the author was about to be discharged from the hospital with a red blood cell count of 4,200,000 when a relapse set in which prolonged her stay in the hospital for nine weeks. If the remission is not very complete and the patient's blood will not show a red blood cell count of over

4,000,000 after prolonged rest in bed, several transfusions judiciously given, and a nourishing diet, a prolonged remission is not to be expected. Such patients are usually quite ill again after two or three months.

In the later stages of the disease remissions are difficult to induce, slow in progress, are not very extensive, and are usually of short duration.

Amelioration of the symptoms arising from the lesions of the nervous system is not to be expected. However hopeful a prognosis for the immediate future circumstances permit in regard to all other features of the case, the nervous symptoms must be excepted. Small variations in the amount of annoyance caused by them may occur, or the patient by a process of unconscious reëducation may learn to compensate somewhat for them, but no real improvement ever takes place. Usually evidence can be adduced to show that these disorders are slowly, it may be, but nevertheless surely, progressing.

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INDEX

A

Abdominal discomfort, 71
Abdominal wall, 79
Abrami, 121
Acetone in urine, 89
Acetylphenylhydrazine, anemia from, 62
Achlorhydria, 51
Achylia gastrica, 26, 36, 53, 58, 72, 90, 109
  in anemia of elderly, 26, 111
    combined sclerosis of spinal cord, 123
  of sprue, 50, 117
  tertiary syphilis and, 115
Acquired hemolytic jaundice, 103
Acute hemorrhage, 17, 20
Acute infections, anemia of, 18, 113
Addis, 25, 44, 90
Addison, 9, 23
Addison's disease, 34, 66
Adrenal glands, 65
Adrenalin, cholesterol and, 66
Age Incidence of Pernicious Anemia, 26
Agglutinins, 138
Albumin, in urine, 88
Alessandri, 66
Alimentary tract, streptococcic infection of, 51
Alkaline reserve, 85
Ames, Wearn, Warren and, 135
Amino-acid content of blood, 85
Anaphylactic shock, hemolysis in, 52
Anatomical changes
  in bone-marrow, 38
  of gastro-intestinal tract, 36
    heart, 36
    intestinal mucosa, 36
    kidneys, 37
    liver, 37
    lungs, 37
    nervous system, 40
    pleura, 37
    spinal cord, 40
    spleen, 37, 56
    stomach, 36
    urogenital tract, 37
Anchylostoma duodenale, 85, 116
Anemia
  blood volume of, 10
  definition of, 10
  from acetylphenylhydrazine, 62
    arsenic, 131
    cobra venom, 52
    diisoprophylhydrazine, 62
    fatty acids, 52
    gastrectomy, 54
    hydro-chloride, 62
    p-oxy-phenyl-ethylamine, 52
    saponin, 52
    soluble soaps, 52
    stricture of intestine, 54
    toluylendiamin, 52, 62
  in infants, 20

Anemia—*continued*
mechanism of production, 15
of children
urobilin excretion, 25
nucleated red blood cells in, 109
elderly, 26, 111
Hodgkin's disease, 120
inanition, 19
leukemia, 119
malignancy, 15
salvarsan poisoning, 119
primary or idiopathic, 12
secondary, 12
Anisocytosis
in anemia of infection, 113
elderly, 111
hemolytic icterus, 121
pernicious anemia, 108
secondary anemia, 98
secondary aplastic anemia, 120
sprue, 118
Anitchkow, 150
Anorexia, 71
Antihemolysis
by cholesterol, 61
serum, 69
after transfusion, 136
Antra, 78
Apathy, 74
Archibold, 144
Arsenic
aplastic anemia from, 131
and neuritis, 83
in treatment of pernicious anemia, 120
Arterio-sclerosis, 87
Ashby, 135
Ashford, 50, 118
Asthenia, 49
Ataxia, 73, 81
Austin, Pepper and, 86, 146

B

Babinski sign, 81
Bacterial flora, of intestines, 53, 54
Bahr, 50
Basophilia, 100
Bass, 25
Batten
and Collier, 41
Risien-Russell, and Collier, 73, 82, 122
Baumann
Mendel and, 66
and Holly, 65
Beckel, 133
Bernheim, 145
Biermer, 9, 23
Bile
and absorption of cholesterol, 67
in stool, 91
pigments after splenectomy, 147
salts of plasma, 86
and nervous lesions, 87
Biliousness, 71
Blankenhorn, 86
Bleeding time, 94
Bloch, 84
Blood
amino acid of, 85
creatinin of, 85
non-protein nitrogen of, 85
picture in pernicious anemia, 93
pigments
metabolism of, 44
plasma nitrogen of, 85
platelets
in hemorrhages, 107

Blood—*continued*
platelets in pernicious anemia, 106
in splenic vein, 55
specific gravity of, 85
sugar, 85, 87
in stool, 91
urea of, 85
uric acid of, 85
in urine, 89
urobilin in, 45
volume
in anemia in general, 10
in pernicious anemia, 93
Blood pressure, 79
Bloomfield, 140, 142, 146
Bloor, 57, 62
and Knudson, 61, 62, 83
McPherson, 64
Bodansky, 62, 131
Bohland, 85
Bone-marrow
anatomical changes, 38
gigantoblasts in, 40
histogenous macrophages, 39
infection of, 46
iron-containing pigment of, 39
iron deposition in, 35
megaloblastic cells in, 39, 40
normoblasts in, 39
phagocytosis in, 67
tumor of, 46
typhoid bacillus from, 51
Bowcock, 135
Brazil, 30
Brittingham, Drinker and, 134, 137
Brown, Peabody and, 67
Brûle, 121
Buzzing in ears, 74
B. welchii, as etiological agent, 51

C

Cachexia
and pernicious anemia, 34
of old age confused with pernicious anemia, 110
Canada, 29
Canal Zone, Panama, 31
Capps, 96
Carcinomatosis, 21, 22, 46, 76, 112
Casts, in urine, 88
Cederberg, 52
Cerebral areas, 82
Chauffard, Laroche and Grigaut, 65
Chlorosis, 14, 17, 20
Cholesterol
in adrenal glands, 65
and adrenalin, 66
as antihemolytic agent, 58
antihemolytic property in blood, 61
and bile, 67
in blood after splenectomy, 58, 62, 84
in whole blood, 61
diminished in pernicious anemia, 69
and medial degeneration, 150
in plasma, 61, 62, 83
in red blood cells, 62
after transfusion, 136
and treatment of pernicious anemia, 149
Cholesterol esters
in plasma, 62
in red blood cells, 62
Cholesterol feeding, 66
Cholesterol oleate, in *Dibothriocephalus latus* anemia, 48

Christian, 76, 87
Chronic hemorrhage, 17
Chronic nephritis, 46, 87
Cirrhosis of liver, 21
Clark and Evans, 58, 60, 136
Classification of Anemia, 11
  on basis of blood formation type, 13
    color index, 11
    megaloblasts, 13
    normoblasts, 13
  of Lazarus, 14
    Naegeli, 15
    Morawitz, 15
Clotting Time in Pernicious Anemia, 94
Cobra-lecithid, 63
Cobra-venom, 52, 56, 63
Cohnheim, 39, 67
Collier
  Risien-Russell, Batten and, 73, 82, 122
  Batten and, 41
Colon, bacterial flora of, 53, 54
Colon bacillus, tyramin from, 52
Color index
  as basis of classification, 11
  explanation of term, 11, 16
  in chlorosis, 17
    hemolytic icterus, 121
    hemorrhagic anemia, 17
    infections with anemia, 18, 113
    malaria, 114
    pernicious anemia, 94, 108
    secondary aplastic anemia, 119
    sprue, 118
Colwell, 143
Combined disseminated sclerosis of spinal cord, 73, 82
Combined disseminated sclerosis of spinal cord—*continued*
  achylia gastrica in, 123
  diarrhea in, 123
  discoloration of skin, 123
  leucopenia in, 123
  paralysis of, 73
  platelets in, 123
Coma, 74
Conjunctiva, 77
Constipation, 50
Cornell, 51
Cranial motor nerves, 74
Creatinin, 85, 88
Csaki, 97
Csonka, 57

D

Dana, 41, 73, 82, 122
Decastello, 32
Delirium, 74
Denis, 61, 84, 146
Denmark, 30
Denny, 93
Denzer, 25
Destruction of Red Blood Cells
  normally, 55, 59
  pathologically, 55
Diacetic acid
  in urine, 89
Diaphragm
  fatty degeneration in, 42
Diarrhea, 50, 71, 72
  controlled by hydrochloric acid, 128
  in combined sclerosis of spinal cord, 123
  of sprue, 50, 117, 118
Dibothriocephalus latus, 47, 48, 68, 85, 116
  cholesterol oleate of, 48

Dickson, 67
Differential White Blood Cell formula, 104
Digestive system symptoms, 70
Diplobacillus, in sputum, 51
Dizziness, 75
Donor, for transfusion, 138, 144
Drinker and Brittingham, 134, 137
Dubin and Pearce, 58
Diisopropylhydrazine hydrochloride, anemia from, 62
Duodenal contents, 90
Duration of Life, in pernicious anemia, 152
Dyspepsia, 71
Dyspnea, 75

E

Ears, 78
Eben, von Stejskal and, 84
Ecchymoses, 35, 77, 89
Edema, 34, 75, 76, 80
Ehrlich, 13
Elders, 51
Emaciation
in pernicious anemia, 34, 75, 76
of sprue, 118
Endocardium, 36
Endothelial macrophages, 37, 38
Endotheliocytes, 106
Endothelium, 37
England, 30
Eosinophile cells, 36
Eosinophilia, 105, 116
Epicardium, 36
Eppinger, 56, 57, 146
Ergot, tyramin from, 52
Esophagus, 72
Esophageal varices, 47
Evans, 131, 139
Clark and, 58, 60, 136
Willson and, 27, 31, 32, 33, 71
Eye, fatty degeneration of, 42

F

Faber, 52, 137, 148
Family Histories, of patients with pernicious anemia, 31
Faust, and Tallquist, 48, 57, 59
Fatiguability, 70
Fatty acids
anemia from, 52
in hemolytic anemias, 57
plasma, 61
saturation of in hemolytic anemias, 61
after splenectomy, 62
unsaturation of in anemia after splenectomy, 57
Fatty degeneration
of diaphragm, 42
eye, 42
intercostal muscles, 42
muscles, 42
Fenwick, 53
Fever
in hemolytic icterus, 120
pernicious anemia, 49, 93, 109, 114
Flaccid paralysis, 81
Flexner and Noguchi, 63
Flint, 53
Focal infections, 134
Formication, 73, 82
Fowler's solution, in treatment of pernicious anemia, 130
Friedenwald and Morrison, 71, 90

G

Gastrectomy, 47, 54
Gastric contents, 89
Gastric mucosa atrophy, 53
Gastro-duodenal ulcers, 47
Gastro-intestinal symptoms, 70, 118, 153
Gastro-intestinal tract, anatomical changes of, 36
Gaucher's disease, 114
Genitalia, 80
Germanium dioxide, in treatment of pernicious anemia, 131
Gettler, and Lindeman, 88
Giffin, 147
  and Szlapka, 147
Gigantoblasts, 40, 101, 155
Girdle sensations, 81
Glossitis, 35
Gorham and Myers, 61, 62, 83
Gorke, 131
Grigaut, 65
  Chauffard, Laroche and, 65
Gudzent, 133
Gums, 72, 78

H

Hackman, Locke and, 103
Haden, 48, 96, 152
Hallucinations, 74
Hammett, Mowery and Muller, 131
Hartman, 54
Headache, 7, 75
Heart, 36, 78
Hedinger and Schlayer, 87
Heeres and Russchen, 56
Hellman, Hess, Weinstock and, 133
Hematopoiesis, 19, 20, 45, 136
Hemic murmur, 78
Hemoglobin, intravenous injection of, 145
Hemolymph nodes, 38
Hemolysis, 18
  and anaphylactic shock, 52
  by cobra-lecithid, 63
    cobra-venom, 56
    hypotonic salt, 56
    mechanical shaking, 56
    oleic acid, 57
    saponin, 56
    soaps, 56
    sodium oleate, 59, 61
    stearic acid, 58
  inhibited by serum, 60
  spleen as factor, 55, 56, 59, 69
  urobilin as index of, 45
Hemolytic extract, from tissues of body, 53, 59
Hemolytic icterus, 21, 55, 80, 120
Hemorrhagic anemia, 21
  platelets in, 107
  nucleated red blood cells in, 109
  shock of, 137
  transfusion in, 141
Hemorrhoids, 47
Hermann, 25
Hess, Weinstock and Hellman, 133
Heuer, 133
Hirayama, 66
Hirschfield, 133
Histogenous macrophages, 37, 39, 106
Hodgkin's disease, 120
Holler, 132
Holly, Baumann and, 65
Horiuchi, 64

Horses, pernicious anemia of, 49
Howland, 25
Huck, 135
Hunter, 51, 52, 133
Hurst, 51
Hyaline changes of vessels
of central nervous system, 40
of spleen, 56
Hydrochloric acid
diarrhea controlled by, 129
in gastric contents, 89
tongue improved by, 129
in treatment of pernicious anemia, 129
Hygienic Conditions, 32
Hypersplenism, 56
Hypotonic salt, hemolysis by, 56

I

Icterus neonatorum, 21
Idiopathic anemia, 21
Ileum, stricture of, 54
Inanition, 19
Indigestion, 71
Infants, anemia in, 20
Infections, 21
anemia of confused with pernicious anemia, 113
of bone-marrow, 46
Intercostal muscles, fatty degeneration of, 42
Intestines
anatomical changes of, 36
bacterial flora of, 54
hemolytic poison in, 52
parasites of, 47
stasis, 47
Iodine
number in hemolytic anemia, 57
Iodine—*continued*
in treatment of pernicious anemia, 132
Ireland, 30
Iron
deposition in organs, 35, 41
metabolism, 16
pigments in bone-marrow, 39
endothelium, 37
Küppfer cells, 37
liver and spleen, 52
in treatment of pernicious anemia, 129
Irritability, 74
Iszard, Muller and, 132
Italy, 30
Iverson, Meulengracht and, 87
Iwao, 52

J

Jaundice, 76
Jewish patients, 30
Joelson and Shorr, 65

K

Kefir, treatment of pernicious anemia, 148
Keidel, Moore and, 131
Kemperer, 133
Kidneys
anatomical changes in, 37
function of, 26, 76, 84, 87
hemorrhages of, 89
iron deposition in, 35
King, 57, 146
Kinnicutt, 53
Kipp, 61, 84, 136
Klotz, 30, 150
Knox, Wahl and Schmeisser, 150

Knudson, 66
Bloor and, 61, 62, 83
Kolmer, 64
Krumbhaar, 147
Küppfer cells, iron pigment in, 37
Kyes, 53

L

Lactic acid, in gastric contents, 90
Ladd, Levine and, 27, 29, 31, 77, 89, 105
Lamar, 58, 59
Laroche, Chauffard, and Grigaut, 65
Lateral columns, 40
Lazarus, 14
Lecithin
in blood after splenectomy, 84
red blood cells, 63
sheaths of nerves, 63
Lee, Minot and, 80, 130, 138, 141, 143
Lehmann, Seyderhelm, and Wichels, 52, 54
Leichtenstern, 122
Leucocytosis, 104, 110, 113
Leucopenia
in anemia of infection, 113
carcinomatosis, 112
diagnosis, 110
elderly, 111
hemolytic icterus, 121
malaria, 114
prognosis, 105
combined sclerosis of spinal cord, 123
sprue, 118
Leukemia
anemia of, 119
Leukemia—*continued*
nucleated red blood cells in, 109
Levine and Ladd, 27, 29, 31, 77, 89, 105
Libman, Ottenberg and, 144
Lichtheim, 122
Lindeman, Gettler and, 85
Lipoids
and red blood cells, 62
in adrenal glands, 65
hemolytic anemias, 64
metabolism of, 43, 64, 83
Liver, 79
anatomical changes in, 37
enlargement of, 49
in hemolytic icterus, 120
iron in, 52
iron deposition in, 35
Locke and Hackman, 103
Locomotor ataxia, 40
Loss of weight, 34, 75, 118
Lungs
anatomical changes, 37
iron deposition in, 35
Lymph glands, 78
anatomical changes, 38
iron deposition in, 35
Lymphoid leukemia, 25

M

MacCallum, 67
MacLachlan, 102
Malaria
color index in, 114
compared to pernicious anemia, 114
history of in pernicious anemia, 33
polymorphonuclear leucopenia in, 114

Malaria—*continued*
spleen in, 114
stomach contents in, 115
tongue in, 115
urobilin in, 114
Malignancy, 21, 22, 34, 46, 76, 112
Maniacal excitement, 74
Manner of Life, in relation to pernicious anemia, 33
Marcora, 51
McPhedran, 58
McPherson, Bloor and, 64
Mechanical shaking, hemolysis by, 56
Megaloblasts, 13, 101
in bone-marrow, 39, 40
prognosis, 155
occurrence in blood, 14
Melancholia, 74
Memory, loss of, 74
Mendel and Baumann, 66
Meningeal hemorrhages, 35
Mercury vapor lamp, in treatment of pernicious anemia, 133
Meulengracht, 54
and Iverson, 87
Metabolism
in pernicious anemia, 84
of hemoglobin, 44, 90
iron, 16
lipoids, 64
nitrogen, 84, 88
urobilin, 44, 90
Milk, treatment of pernicious anemia, 52, 148
Minot, 86, 146
and Lee, 80, 130, 138, 141, 143
Sellards and, 139
Mohr, 84
Monilia in sprue
albicans, 50, 118
psilosis, 50, 118
Mononuclear cells, 106
Moore and Keidel, 131
Morawitz, 15
Morrison, Friedenwald and, 71, 90
Mosenthal, 86, 87, 128
Mouth, 78
Mowery, Hammett, and Muller, 131
Moynihan, 54
Mucous membranes, 72, 76
Mueller, 66
Muller
and Iszard, 132
Hammett, Mowery and, 131
Muscles
fatty degeneration of, 42
iron containing pigment, 41
iron deposition in, 35
Musser, 130
Myeloblastic leukemia, 20
Myelocytes, 38, 57, 106
Myers, Gorham and, 61, 62, 83

N

Naegeli, 15
Nausea, 71
Negroes, 28
Nerve plexuses, 36
Nerve system
and bile salts, 87
hyaline changes of vessels, 40
injury of, 157
physical findings, 80
prognosis, 157
Neuritis, 83, 118
Nitrogen metabolism, 84, 86, 88
Noguchi, Flexner and, 63

Normoblasts
in bone-marrow, 39
occurrence in blood, 14, 100
in prognosis, 14, 155
Nose, 78
Nucleated Red Blood Cells
in carcinomatosis, 112
infections, 113
hemolytic icterus, 121
pernicious anemia
of diagnostic import, 14, 100, 108
in prognosis, 14, 100, 155
Numbness of hands or feet, 73

O

Oestridae, in pernicious anemia of horses, 49
Oleic acid
hemolysis by, 57
as hemolytic agent, 59
Oliver, 50
Ophthalmoscopic examinations, 77
Optic disk, 77
Osler, 27
Ottenberg and Libman, 144
Oxygenation, in pernicious anemia, 34

P

Pallor, 75
Palpitations, 75
Pancreatic insufficiency, in sprue, 50
Panniculus, 79
Papillary atrophy
in pernicious anemia, 35, 78
sprue, 117
tertiary syphilis, 115
Paralysis, in sclerosis of spinal cord, 73
Parasites in stool, 91
Parasitic infestations, 21, 110
Paresthesias, 81
Pathological lymphocytes, in pernicious anemia, 106
Peabody and Brown, 67
Pearce, 56
Dubin and, 58
Pericardium, 35
Peritoneum, 35
Pepper and Austin, 86, 146
Peptone, treatment of pernicious anemia, 148
Petechiae, 35, 77, 89
Peters and Rubnitz, 85
Phagocytosis, 57, 67
Phenylhydrazine, anemia from, 131
Phillipine Islands, sprue in, 50
Phthisis, 46
Pijper, 96
Piney, 102
Plasma
cholesterol in, 62, 83
fatty acids in, 61
index, 86
nitrogen of, 85
volume, 93
Platelets
in the elderly, 45
hemorrhagic anemia, 107
parasitic anemia, 116
combined sclerosis of spinal cord, 123
affected by transfusion, 134
Pleura, 35, 37
Plesch, 133
Pneumonia, history of in pernicious anemia, 33

Poikilocytosis, 98, 108
in the elderly, 111
hemolytic icterus, 121
anemia of infection, 113
secondary anemia, 98
secondary aplastic anemia, 120
spleen, 38
sprue, 118
Polychromasia, 99
in the elderly, 111
hemolytic icterus, 121
anemia of infection, 113
sprue, 118
Polycythemia vera, as transfusion donor, 144
Polymorphonuclear cells—see under leucocytosis and leucopenia
Posterior columns, 40
P-oxy-phenyl-ethylamine, anemia from, 52
Precordial distress, 74
Pregnancy, anemia in, 21, 47, 119
Premature infants, anemia of, 20
Pribram, Reicher and, 149
Primary Aplastic Anemia, 19, 20
Primary or Idiopathic Anemias, 12
Proescher, 133
Prognosis, in Pernicious Anemia, 152
Prolonged fevers, 46
Protein diet, in treatment of pernicious anemia, 128
Protein shock
after transfusion, 136
treatment in pernicious anemia, 149
Pulse, 79
Purpura, 25
Putrefying meat, tyramin from, 52
Pyloric stenosis, 47
Pyogenic infection, 110
Pyorrhea, 78

R

Racial considerations, 28
Radium, in treatment of pernicious anemia, 133
Rahtjen, 51
Ransom, 63
Rectum, 80
Red Blood Cells
and cholesterol, 62
destruction of normally, 55, 59
pathologically, 55
and lecithin, 62
life after transfusion, 135
resistance of, 56
phagocytosis of, 57
size in pernicious anemia, 96
in splenic vein, 56, 69
Red Blood Cell Counts, in pernicious anemia, 97
Reflexes, 81
Reicher and Pribram, 149
Remission, 156
Resistance of Red Blood Cells, 121
Rest in bed, in treatment of pernicious anemia, 128
Reticulation of Red Blood Cells, 102, 121
Reticulo-endothelial Cells, 37, 57, 67
Retinal hemorrhages, 74
Risien-Russell, Batten and Collier, 73, 82, 122

Riess, 67
Robertson, 44, 55, 90
Robscheit and Whipple, 128, 130
Roentgen-ray treatment, 133
Rogers, 50
Romanowski stain, 100
Rosenquist, 84
Rothschild, 65
Rubnitz, Peters and, 85
Russchen, Heeres and, 56
Russia, 29

S

Salvarsan
  in treatment of pernicious anemia, 130
  poisoning—anemia of, 119
Saponin, 52
Saturation index of Haden, 96
Scandinavian countries, 30
Schaumann and Tallquist, 48
Schlayer, Hedinger and, 87
Schmeisser, Knox, Wahl and, 150
Schneider, 44, 90
Secondary anemias, 12, 119
Sellards and Minot, 139
Sensory disturbances, 73
Serum, antihemolytic power of, 60, 69
Sex distribution, 26
Seyderhelm, 49, 52
  Lehmann and Wichels, 52, 54
Shaumann and Tallquist, 48
Sheaths of nerves, 41, 63
Shorr, Joelson and, 65
Sinuses, 78
Skin, 34, 49
Sleeplessness, 74
Smith, 50
Soaps, hemolysis by, 52, 69
Social conditions of patients, 32
Sodium cacodylate, in treatment of pernicious anemia, 130
Sodium oleate, hemolysis by, 59, 61
Sore mouth, 71, 72
Soreness of tongue, 153
Spastic paralysis, 81
Specific gravity of blood, 85
Speech, disturbances of, 74
Sphincter control, 81
Spinal cord, 40, 73, 81, 122
Spleen, 79
  anatomical changes in, 37, 56
  enlargement of, 49
  as factor in hemolysis, 55, 56, 59, 69
  in hemolytic icterus, 120
  immature myeloid cells in, 38
  iron deposition in, 35, 52
  in malaria, 114
  myeloid cells in, 57
  in parasitic anemia, 116
  phagocytosis in, 57
  poikilocytosis in, 38
  splenomegaly, 109
  in sprue, 117
  tertiary syphilis of, 115
  tuberculosis of, 114
  typhoid bacillus in, 51
Splenectomy, 56
  cholesterol in blood after, 58, 62, 84
  saturation of fatty acids after, 58, 62
  in hemolytic anemias, 56
  nitrogen retention after, 86
  operative mortality in, 147
  in treatment of pernicious anemia, 146
Splenic vein blood, 55, 69
Sprue, 47, 50, 68, 117

Sputum, diplobacillus, 51
Stansfeld, 135
Stearic acid
  hemolysis by, 58
Stengel, 27, 132
Stieglitz, 87
Stomach
  anatomical changes, 36
  contents—see under achylia
  fat absorption from, 66
  disturbances of, 71
Stool, 91, 118
Strauss, 84
Streptococcic infection, of alimentary tract, 51
Stricture, of ileum, 54
Stricture of intestine, anemia from, 54
Subacute combined sclerosis of spinal cord, 41, 122
Subcutaneous fat, 34, 36
Sugar
  in blood, 85
    urine, 89
Swiss cheese, tyramin from, 52
Sweden, 30
Syphilis, 22, 28, 47
  anemia of, 92
  compared with pernicious anemia, 114
Syringomyelia, 81
Szlapka, Giffin and, 147

T

Tabes dorsalis, 81
Tallquist, 85
  Faust and, 48, 57, 59
  Shaumann and, 48
Teeth, 78
Temperature, 92
Tertiary syphilis, 115
Thorium X, in treatment of pernicious anemia, 138
Throat, 78
Thyroid, in pernicious anemia, 78, 132
Tingling of hands and feet, 73, 82
Toluylendiamin, anemia from, 52, 62
Tongue, 35, 72, 78
  improved by hydrochloric acid, 129
  in malaria, 115
  of sprue, 35, 50, 117, 118
Transfusion
  benefit from, 140, 144
  contraindication of, 137
  donors for, 144
  in hemorrhagic anemia, 141
  reactions from, 134, 137
  size of, 142
Transitional Cells, 106
Traumatic shock, transfusion in, 137, 141
Tropics, 30
Tuberculosis, of spleen, 114
Tumor, of bone-marrow, 46
Turk, 60
Typhoid bacillus
  in bone-marrow in pernicious anemia, 51
    spleen in pernicious anemia, 51
Tyramin, 52, 68
Tyrosin, tyramin from, 52

U

Ulcers
  of buccal mucous membrane, 78
    tongue, 78

Umber, 84
Urea, 85, 88
Uric acid, 85, 88
Urine, 88
  acetone in, 89
  albumin in, 88
  blood in, 89
  casts in, 88
  diacetic acid in, 89
  hemoglobin, 89
  nitrogen in, 86
  sugar in, 89
  urobilin in, 45, 88
Urobilin
  as index of hemolysis, 113
  in bile, 44
    blood, 45
    children, 25
    duodenal contents, 90
    the elderly, 112
    hemolytic icterus, 120
    malaria, 114
    metabolism, 44, 90
    stool, 91
    urine, 45, 88
Urobilinogen
  in intestines, 45
    stool, 91
Urogenital tract, anatomical changes in, 37

V

van der Scheer, 51
Vannini, 85
Vessels
  of spinal cord, 40
    spleen, 56
Vision, disturbance of, 74
Vitamin deficiency, in sprue, 51
Vogel, 147
Volume index of Capps, 96
Vomiting, 71
von Noorden, 84, 133
von Stejskal and Eben, 84

W

Wahl, Knox, and Schmeisser, 150
Warren, Wearn, and Ames, 135
Wassermann Test, 91
Weakness, 70, 73, 82, 118
Wearn, Warren and Ames, 135
Weinstock, Hess, and Hellman, 133
Whipple and Robscheit, 128, 130
White Blood Cell Counts—see under leucocytosis and leucopenia
Wichels, Seyderhelm, Lehmann and, 52, 54
Widal, 121
Wilbur, 25
Will power, weakness of, 74
Willson and Evans, 27, 31, 32, 71
Wood, 50

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